Title
Design of Cruzain Inhibitors for the Treatment of Chagas Disease AND Development and Application of Methods for the Asymmetric Synthesis of α-Branched Amines

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Design of Cruzain Inhibitors for the Treatment of Chagas Disease

AND

Development and Application of Methods for the Asymmetric Synthesis of α-Branched Amines

by

Katrien Brak

A dissertation submitted in partial satisfaction of the

requirements for the degree of

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in

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in the

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of the

University of California, Berkeley

Committee in charge:

Professor Jonathan A. Ellman, Chair
Professor Carolyn R. Bertozzi
Professor Jasper Rine

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Abstract

Design of Cruzain Inhibitors for the Treatment of Chagas Disease

AND

Development and Application of Methods for the Asymmetric Synthesis of α-Branched Amines

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Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Jonathan A. Ellman, Chair

Chapter 1. The development of inhibitors of cruzain, the major cysteine protease of the *Trypanosoma cruzi* parasite that causes Chagas disease, has been demonstrated to be a promising drug discovery avenue for the treatment of this neglected disease. The development of a new class of potent nonpeptidic inhibitors of cruzain is described. Application of the substrate activity screening method to cruzain resulted in the identification of a nonpeptidic substrate. Guided by a molecular replacement model, substrate cleavage efficiency was further improved by introducing additional binding interactions. The optimized substrates were then converted to inhibitors by the introduction of cysteine protease mechanism-based pharmacophores. This led to the development of a new class of nonpeptidic 2,3,5,6-tetrafluorophenoxymethyl ketone inhibitors that exhibit potent inhibitory activity against cruzain. It was also established that this class of compounds completely eradicates the *T. cruzi* parasite from mammalian cell culture and substantially ameliorates symptoms of acute Chagas disease in a mouse model with no apparent toxicity. These results suggest that nonpeptidic tetrafluorophenoxymethyl ketone cruzain inhibitors have the potential to fulfill the urgent need for improved Chagas disease chemotherapy.

Chapter 2. A high-resolution crystal structure confirmed the mode of inhibition and revealed key binding interactions of the novel nonpeptidic tetrafluorophenoxymethyl ketone cruzain inhibitor class identified in Chapter 1. Subsequent structure-guided optimization then resulted in inhibitor analogs with improvements in potency despite minimal or no additions in molecular weight. Evaluation of these second-generation tetrafluorophenoxymethyl ketone cruzain inhibitors in cell culture is also described.

Chapter 3. The rhodium(I)-catalyzed addition of alkenylboron reagents to imines is described. The diastereoselective addition of alkenyl trifluoroborates and MIDA boronates to both aromatic and aliphatic *N*-*tert*-butanesulfinyl aldimines provides α-branched allylic amines in good yields and with very high selectivity. The chemistry is demonstrated to be compatible with a variety of electronically and sterically diverse *N*-sulfinyl imines and alkenyl boron reagents. This new methodology enables the general and efficient asymmetric synthesis of the important class of α-branched allylic amines from readily available and stable starting materials. Also included is a preliminary investigation into the enantioselective addition of alkenylboron reagents to activated imines.

Chapter 4. A one-pot preparation of *N*-*tert*-butanesulfinylamine diastereomer mixtures that proceeds in excellent yields for a diverse set of *N*-sulfinyl imine addition products is described. The method is operationally simple, and extractive isolation provides analytically pure mixtures of diastereomers as standards for stereoselectivity determinations. This method enabled the rapid and accurate determination of diastereomeric purity of the *N*-sulfinylamines prepared in Chapters 3 and 5.

Chapter 5. The concise total synthesis of (–)-aurantioclavine has been achieved by taking advantage of strategies for the asymmetric alkenylation of *N*-*tert*-butanesulfinyl imines. The enantiomerically pure natural product was prepared both by using the Rh-catalyzed addition of a MIDA boronate developed in Chapter 3 and by employing a Grignard reagent addition sequence. Exploration of (–)-aurantioclavine's role as an intermediate en route to the complex polyclic alkaloids of the communesin family is also described.

Table of Contents

Acknowledgments

First and foremost, I would like to thank Professor Jonathan Ellman for being a great mentor. Over the last five years, Jon instilled in me the value of rigor in scientific work as well as the importance of developing useful chemistry, which I hope will stay with me throughout the rest of my scientific career. Jon's enthusiasm for science was contagious and never failed to amaze me. I will always be grateful for his encouragement, attention to detail, and forthright personality.

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And last but not least, there is Nathan, who I would like to thank for his unwavering love and support. Sometimes I wonder if I would have made it through these five years without him. Thanks for listening to me all these years and for accepting me for who I am. Our Sunday adventures mushroom hunting, hiking, playing tennis, cooking good food are what got me through the weeks. I am truly looking forward to our exciting times ahead.

Chapter 1. Identification of a New Class of Nonpeptidic Inhibitors of Cruzain for the Treatment of Chagas Disease.

A century after discovering that the Trypanosoma cruzi (T. cruzi) parasite is the etiological agent of Chagas disease, treatment is still plagued by limited efficacy, toxicity, and the emergence of drug resistance. The development of inhibitors of the major T. cruzi cysteine protease, cruzain, has been demonstrated to be a promising drug discovery avenue for this neglected disease. This chapter describes the development of a new class of potent nonpeptidic inhibitors of cruzain. The substrate activity screening (SAS) method, a substrate-based method for the identification and optimization of enzyme inhibitors, was used to screen a library of protease substrates initially designed to target the homologous human protease cathepsin S. Structure-based design was next used to further improve substrate cleavage efficiency by introducing additional binding interactions in the S3 pocket of cruzain. The optimized substrates were then converted to inhibitors by the introduction of cysteine protease mechanism-based pharmacophores. Incorporation of the vinyl sulfone pharmacophore resulted in a reversible inhibitor even though this pharmacophore is well documented to give irreversible cruzain inhibition for peptidic inhibitors. The previously unexplored β-chloro vinyl sulfone pharmacophore provided mechanistic insight that led to the development of potent irreversible acyl- and aryl-oxymethyl ketone cruzain inhibitors. For these inhibitors, potency did not solely depend on leaving group pK_a, with a 2,3,5,6-tetrafluorophenoxymethyl ketone inhibitor identified as one of the most potent inhibitors with a second-order inactivation constant of 147,000 $s^{-1} M^{-1}$. It was also established that this inhibitor completely eradicates the T. cruzi parasite from mammalian cell culture and substantially ameliorates symptoms of acute Chagas disease in a mouse model with no apparent toxicity. These results suggest that nonpeptidic tetrafluorophenoxymethyl ketone cruzain inhibitors have the potential to fulfill the urgent need for improved Chagas disease chemotherapy. The majority of this work was published in full papers (Brak, K.; Doyle, P. S.; McKerrow, J. H.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6404-6410 and Brak, K.; Kerr, I. D.; Barrett, K. T.; Fuchi, N.; Debnath, M.; Ang, K.; Engel, J. C.; McKerrow, J. H; Doyle, P. S.; Brinen, L. S.; Ellman, J. A. *J. Med. Chem.* **2010**, 53, 1763-1773).

Authorship

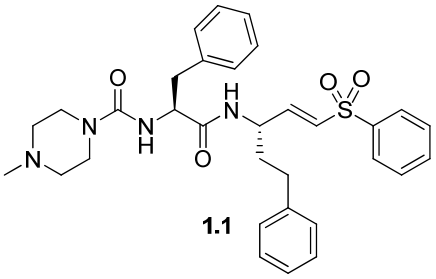
This work was conducted in collaboration with Dr. Patricia Doyle and Prof. James McKerrow. Dr. Doyle performed the cell culture and animal studies at the Sandler Center for Basic Research in Parasitic Diseases at the University of California, San Francisco.

Introduction

Chagas disease (American trypanosomiasis), caused by the parasitic protozoan *Trypanosoma cruzi (T. cruzi)*, is the leading cause of heart disease in Latin America. Today, at least 15 million people are infected with the parasite, resulting in more than 12,000 deaths each year.[1] Chemotherapy for Chagas disease is unsatisfactory because the current drugs, nifurtimox and benznidazole, have significant toxic side effects.[2] Due to the toxicity of current chemotherapy and emerging drug resistance, there is an urgent need for developing an effective therapy against Chagas disease.

Cruzain, a cysteine protease of the papain family, is the primary cysteine protease of the *T. cruzi* parasite. It is involved in intracellular replication and differentiation and is essential at all stages of the parasite's life cycle.[3] Recently, it has been demonstrated that *T. cruzi* infection can be cured in cell, mouse, and dog models by treatment with irreversible inhibitors of cruzain.[4,5] Parasite vulnerability to cruzain inhibition results from the lack of redundancy of this enzyme. Moreover, parasite localization provides a means for preferential inhibition of cruzain over the highly homologous human papain superfamily cysteine proteases cathepsins B, L, K, S, F and V because the parasite resides in the host cell cytoplasm whereas the cathepsins are located in the less accessible lysosomes.[6] For these reasons, cruzain is a highly attractive therapeutic target for the treatment of Chagas disease.[7]

Dipeptidyl vinyl sulfone **1.1** is the most advanced inhibitor of cruzain and is currently in pre-clinical trials (Figure 1.1).[8] Although this peptidic inhibitor has shown good efficacy with minimal toxicity, nonpeptidic inhibitors with improved oral bioavailability could prove even more effective. Because only irreversible inhibitors of cruzain have been successful in curing parasitic infections, we sought to develop nonpeptidic irreversible inhibitors of cruzain.[9]



1.1

Figure 1.1. Most advanced inhibitor of cruzain.

Recently, we developed Substrate Activity Screening (SAS) as a new method for the rapid identification of nonpeptidic enzyme inhibitors.[10-13] The SAS method consists of the following steps: identification of nonpeptidic substrate fragments, substrate optimization, and conversion of optimal substrates to inhibitors. Significantly, the SAS method has successfully been applied to the papain superfamily protease cathepsin S,[10,12,13] which has high homology to cruzain.[14] Using

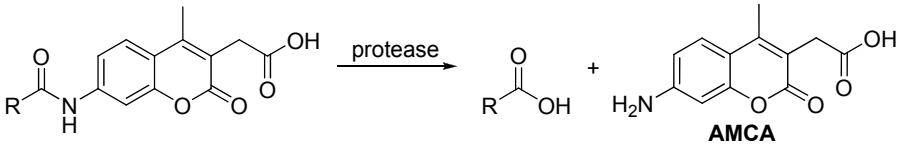
a focused substrate library developed for cathepsin S as a starting point, we report herein the development of a new class of nonpeptidic 2,3,5,6-tetrafluorophenoxymethyl ketone inhibitors that exhibit potent inhibitory activity against cruzain. Furthermore, we demonstrate that this class of compounds completely eradicates *T. cruzi* parasites in cell culture and greatly improves symptoms of acute Chagas disease in a mouse model. Tetrafluorophenoxymethyl ketone inhibitors therefore represent a promising and novel inhibitor class for the treatment of Chagas disease.

Identification and Optimization of Cruzain Substrates

Initial Screening

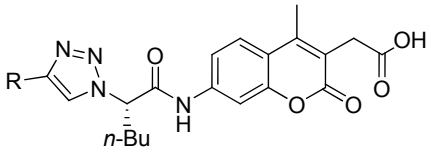
High correlation between substrate cleavage efficiency and inhibitory activity was observed in the previous development of cathepsin S inhibitors.[10,12] Substrate analogs were therefore first evaluated and optimized before conversion to inhibitors. A triazole-based substrate library consisting of more than 150 substrates was screened against cruzain. Substrate activity was measured by monitoring liberation of the 7-amino-4-methyl coumarin acetic acid (AMCA) fluorophore, which results from protease-catalyzed amide bond hydrolysis (Scheme 1.1).

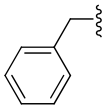
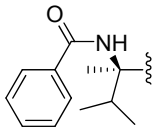
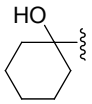
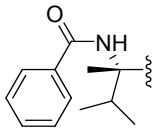
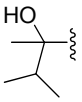
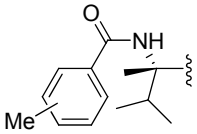
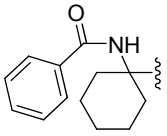
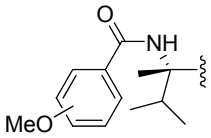
Scheme 1.1. Fluorogenic substrate screening



Shown in Table 1.1 is the structure activity relationship (SAR) for a subset of substrates from the triazole library that exemplifies cruzain's substrate specificity requirements.[15] The weakest substrate for which a signal could be detected was substrate **1.2** that incorporated a simple benzyl substituent on the triazole ring. A variety of more active hydroxyl substituted substrates were screened and the optimal aliphatic functionalities identified were the methyl and isopropyl substituents present in substrate **1.4**. Replacement of the hydroxyl group of **1.3** with a benzamide moiety in substrate **1.5** resulted in an increase in cleavage efficiency. The epimeric compounds **1.6** and **1.7** demonstrate that cruzain shows strong chiral recognition with epimer **1.7** being much more active. Substitutions on the benzamide moiety indicated that ortho substituents were not tolerated by cruzain (substrates **1.8** and **1.11**). In contrast, meta and para substituents resulted in increases in substrate activity (substrates **1.9, 1.10** and **1.12**, **1.13**) with *p*-methoxy substituted benzamide substrate **1.13** identified as the most efficient substrate from the screening of the initial triazole library.

Table 1.1. Representative substrates from the 1,2,3-triazole library



cmpd	R	rel. k_{cat}/K_m	cmpd	R	rel. k_{cat}/K_m
1.2		0.00047	**1.6**		0.0074
1.3		0.011	**1.7**		1.0
1.4		0.068	**1.8** **1.9** **1.10**		*o* = 0.41 *m* = 1.8 *p* = 2.0
1.5		0.16	**1.11** **1.12** **1.13**		*o* = 0.22 *m* = 2.0 *p* = 2.8

Structure-Guided Substrate Optimization

Further optimization of substrate binding to cruzain was accomplished using structure-based design. Recently, a crystal structure was obtained of chloromethyl ketone inhibitor **1.14** bound to cathepsin S.[12] The amino acid sequences of cathepsin S and cruzain are 38% homologous and their active sites nearly identical (Figure 1.2).[14] Taking into account the high homology between these two enzymes, molecular replacement was performed to model inhibitor binding to cruzain (Figure 1.3).

```
Cathepsin S    2  PDSVDWREKG CVTEVKYQGS CGACWAFSAV GALEAQLKLK TGKLVSLSAQ
Cruzain        2  PAAVDWRARG AVTAVKDQGQ CGSCWAFSAI GNVECQWFLA GHPLTNLSEQ
                  * .**** .*  ** ** **  **.******. * .* *  *     * .** *

Cathepsin S   52  NLVDCSTEKY GNKGCNGGFM TTAFQYIID- NK-GIDSDAS YPYKAM---D
Cruzain       52  MLVSCDK--- TDSGCSGGLM NNAFEWIVQE NNGAVYTEDS YPYASGEGIS
                   ** *       . **.**.*   **. *..  *. .. .. * *** .

Cathepsin S   97  QKCQYDSKYR AATCSKYTEL PYGREDVLKE AVANKGPVSV GVDARHPSFF
Cruzain       92  PPCTTSGHTV GATITGHVEL PQ-DEAQIAA WLAVNGPVAV AVDASS--WM
                    *   .    .** .   ** *   *  .   .* .***.* .***

Cathepsin S  147  LYRSGVYYEP SCTQNVNHGV LVVGYGDLNG KEYWLVKNSW GHNFGEEGYI
Cruzain      143  TYTGGVMTS- CVSEQLDHGV LLVGYNDSAA VPYWIIKNSW TTQWGEEGYI
                   * .**       . ..***  *.*** *  .   **..****      ******

Cathepsin S  197  RMARNKGNHC GIASFPSYPE I
Cruzain      188  RIAKGS-NQC LVKEEASSAV VG
                  *.*.  *.*  .  .* .  .
```

Figure 1.2. Alignment of cathepsin S (PDB ID 2H7J) and cruzain (PDB ID 1F2C) amino acid sequences with areas around the catalytic triad highlighted in yellow. Identical residues are indicated with " * " and similar residues are indicated with " . ". The figure was produced using Swiss-Pdb Viewer (http://ca.expasy.org/spdbv/).

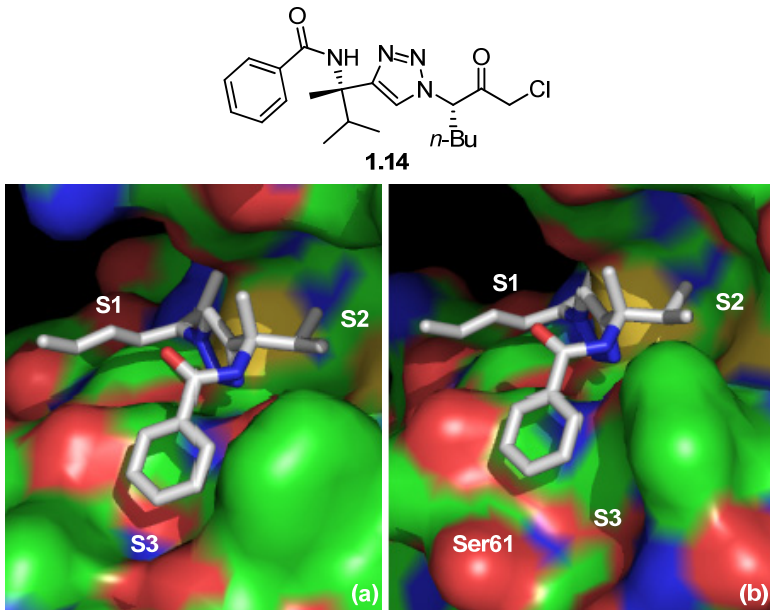


Figure 1.3. (a) Crystal structure of cathepsin S (PDB ID 2H7J) and (b) molecular replacement model of cruzain (PDB ID 1F2C) with chloromethyl ketone inhibitor **1.14**. The atoms are shaded according to element: protein carbons are green, inhibitor carbons are grey, nitrogens are blue, and oxygens are red. The figure was produced using PyMOL (www.pymol.org).

Due to the similarities in the active sites, the inhibitors are predicted to bind in a similar fashion with the *n*-butyl group in the S1 pocket, the methyl and isopropyl groups in the S2 pocket, and the benzamide moiety in the S3 pocket. The majority of prior inhibitor development for cruzain has focused on the S1', S1, and S2 pockets. The S3 pocket of cruzain is largely unexplored with no previous reports of significant binding interactions in this pocket. Upon closer inspection of our molecular replacement model, key differences in the S3 pockets were noted. The S3 pocket of cathepsin S is small and well-defined whereas that of cruzain is large and open-ended. To take advantage of cruzain's larger S3 pocket, a focused library of substrate analogs incorporating planar heterocycles in place of the phenyl ring of the benzamide moiety was designed. Heterocycles were chosen based on their potential for hydrophobic interactions with the hydrophobic side of the pocket and potential for hydrogen bonding interactions with the serine residue in the S3 pocket.

The synthesis of the 1,4-disubstituted-1,2,3-triazole substrates containing the AMCA fluorophore was accomplished on solid support (Scheme 1.2). A 1,3-dipolar cycloaddition of support-bound azide **1.15** and propargyl amine **1.16**, followed by acylation or reductive amination of the resulting support-bound triazole intermediate **1.17**, and cleavage from support, afforded the 1,2,3-triazole substrates as single diastereomers. We were pleased to find that all but one of the substrates of the focused library were more active than the unsubstituted benzamide substrate **1.7** (Table 1.2). The most potent substrates identified were quinoline **1.33** and benzothiazole **1.34** with 7-9 fold increases in cleavage efficiency. These substrates both contained a nitrogen atom para to the amide bond, which could be interacting with the serine residue in the S3 pocket (Figure 1.3b). When comparing naphthyl **1.21** and quinoline **1.33**, a 4-fold increase in activity was observed presumably due to this polar interaction. Moreover, the 4-fold increase in cleavage efficiency of indole **1.31** relative to benzotriazole **1.22** and isatin **1.19**

demonstrated that hydrophobic interactions also contribute to binding. Building deeper into the S3 pocket with substrates **1.29** and **1.32** resulted in no further increases in cleavage efficiency. Substrate **1.18** incorporating a morpholine moiety was prepared because this substituent has led to potent vinyl sulfone inhibitors of cruzain.[16] However, this substituent resulted in a decrease in substrate cleavage efficiency.

Scheme 1.2. General synthesis 1,2,3-triazole substrates for the focused library

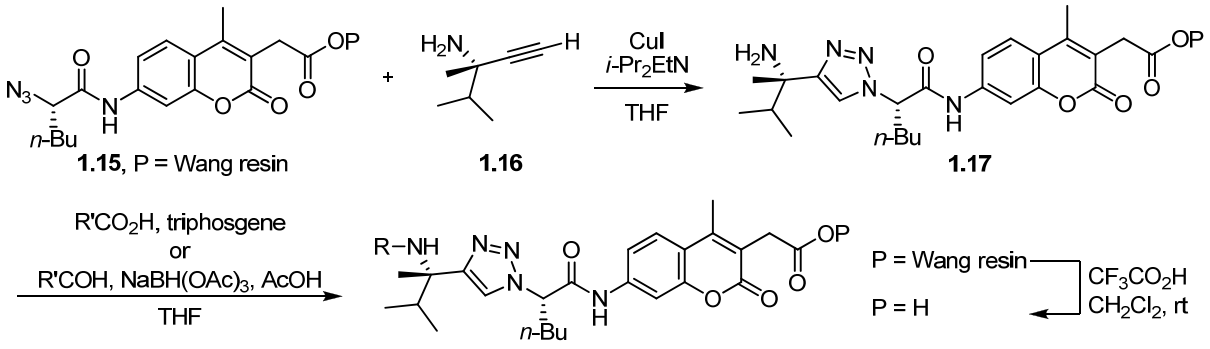
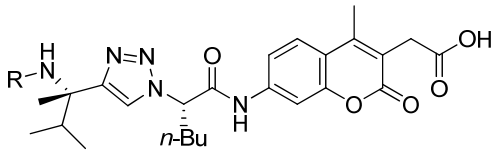


Table 1.2. Cleavage efficiencies of 1,2,3-triazole amide substrates against cruzain



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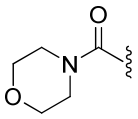
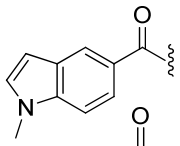
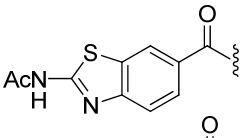
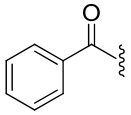
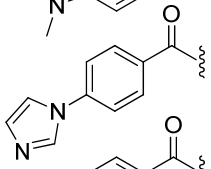
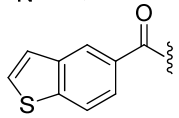
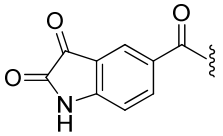
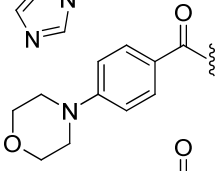
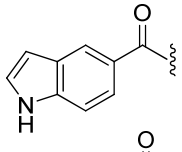
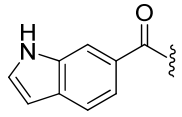
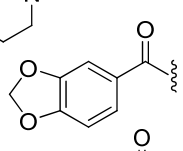
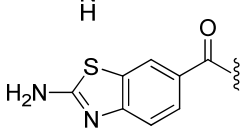
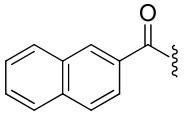
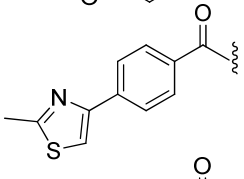
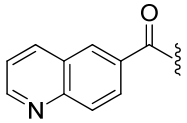
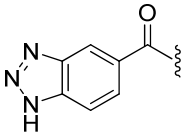
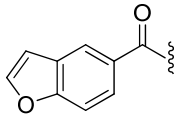
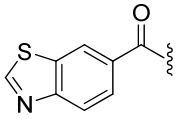
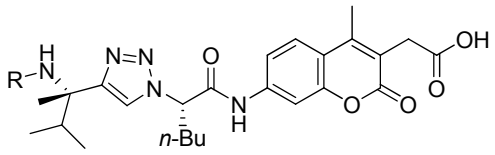
1.18		0.6	**1.23**		2.5	**1.29**		3.9
1.7		1.0	**1.24**		2.8	**1.30**		5.3
1.19		1.3	**1.25**		3.0	**1.31**		6.5
1.20		1.4	**1.26**		3.1	**1.32**		8.0
1.21		1.6	**1.27**		3.3	**1.33**		8.2
1.22		1.7	**1.28**		3.6	**1.34**		9.0

A notable feature in the inhibitor binding model is the nonessential nature of the benzamide carbonyl (Figure 1.3b). Therefore, amine **1.36** corresponding to benzamide substrate **1.7** was prepared resulting in a 3-fold increase in cleavage efficiency (Table 1.3). To determine if amine substrate SAR correlated with the SAR trends observed for the corresponding amide substrates, additional amine analogs were synthesized and evaluated. High correlation was observed between the SAR for the amide and amine substrate series, resulting in the identification of quinoline amine substrate **1.39** and benzothiazole amine substrate **1.40** with 19-fold greater cleavage efficiency than unsubstituted benzamide **1.7**.

Table 1.3. Comparison of 1,2,3-triazole amide and amine substrate activity against cruzain



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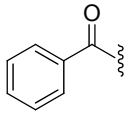
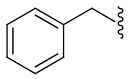
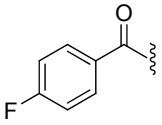
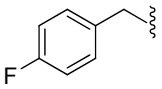
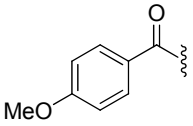
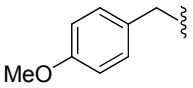
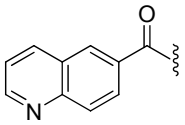
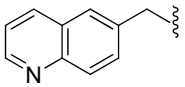
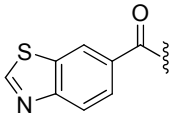
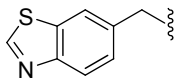
1.7		1.0	**1.36**		3.5
1.35		1.3	**1.37**		4.0
1.13		2.8	**1.38**		6.5
1.33		7.4	**1.39**		19
1.34		9.0	**1.40**		19

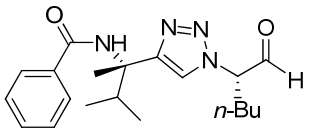
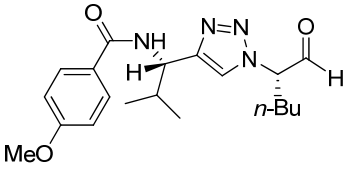
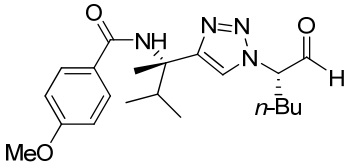
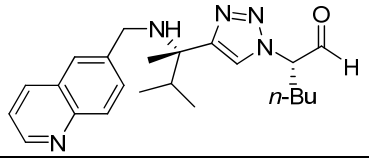
Conversion of Optimized Substrates to Inhibitors

Correlating Substrate Activity to Inhibitor Potency

A key advantage of the SAS method is that the aminocoumarin group has to be precisely oriented in the active site for amide bond hydrolysis to occur and can therefore be directly replaced with mechanism-based pharmacophores. Based on transition-state theory, a correlation between $\log(K_m/k_{cat})$ and $\log(K_i)$ is expected for inhibitors in a related chemical series.[17] For both nonpeptidic aldehyde[10] and nitrile[12] inhibitors of cathepsin S correlation between substrate activity and inhibitor potency has been established. For cruzain, trends in substrate activity were

also found to match aldehyde inhibitor potency (Table 1.4). When the kinetic data was analyzed according to equation 1.1, good correlation was observed (R^2 = 0.94; Figure 1.4). This confirmed that substrate optimization followed by conversion of the optimal substrates to inhibitors is a valid approach for the identification of potent cruzain inhibitors.

Table 1.4. Inhibition of cruzain by 1,2,3-triazole aldehyde inhibitors

aldehyde inhibitor		K_i (μM)
	**1.41**	2.70 ± 0.10
	**1.42**	2.40 ± 0.16
	**1.43**	1.60 ± 0.04
	**1.44**	0.14 ± 0.01

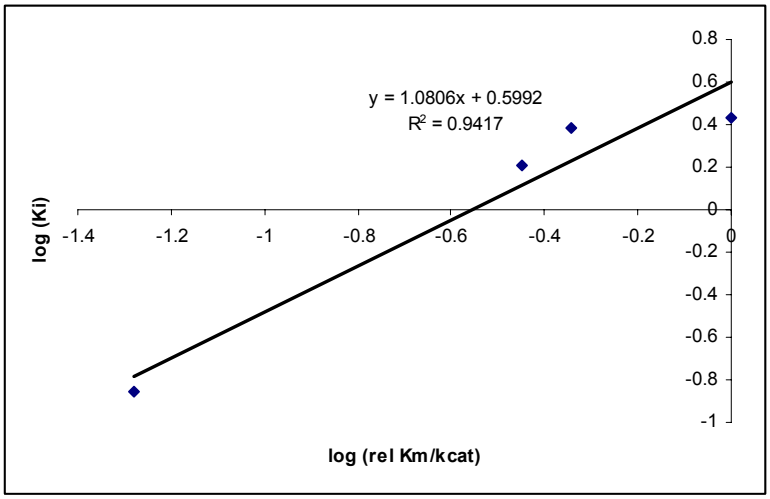
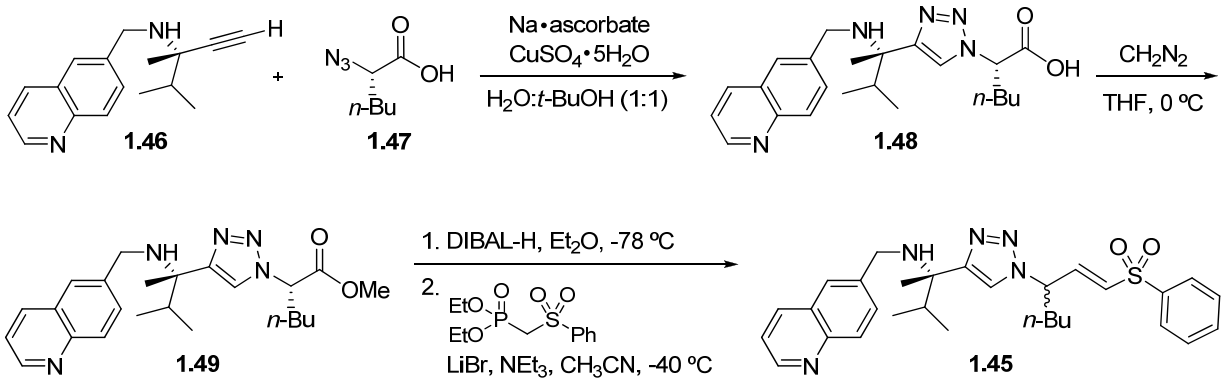


Figure 1.4. Correlation of substrate and inhibitor activity according to equation 1.1: [log(Ki) = log (K_m/k_{cat}) + log (d x k_{uncat})]. Plot of log (K_i) vs. log (K_m/k_{cat}) for 1,2,3-triazole substrates and corresponding aldehyde inhibitors with cruzain.

Conversion to Vinyl Sulfone Inhibitors

In an effort to identify a potent irreversible inhibitor of cruzain, the effectiveness of different cysteine protease mechanism-based pharmacophores was evaluated by converting the optimal quinoline amine substrate **1.39** to a variety of inhibitors. We initially chose to investigate the vinyl sulfone pharmacophore because it has been incorporated in potent inhibitors of cruzain that have proven effective at eradicating Chagas disease in both cell culture and animal models.[4,5,16,18] Vinyl sulfone inhibitor **1.45** was prepared via methylation of carboxylic acid **1.48**, reduction to the aldehyde and subsequent Horner-Wadsworth-Emmons olefination (Scheme 1.3). Kinetic analysis of the vinyl sulfone inhibitor, surprisingly, indicated no time dependence and was consistent with competitive reversible inhibition (Figure 1.5a).[19]

Scheme 1.3. Synthesis of vinyl sulfone inhibitor **1.45**



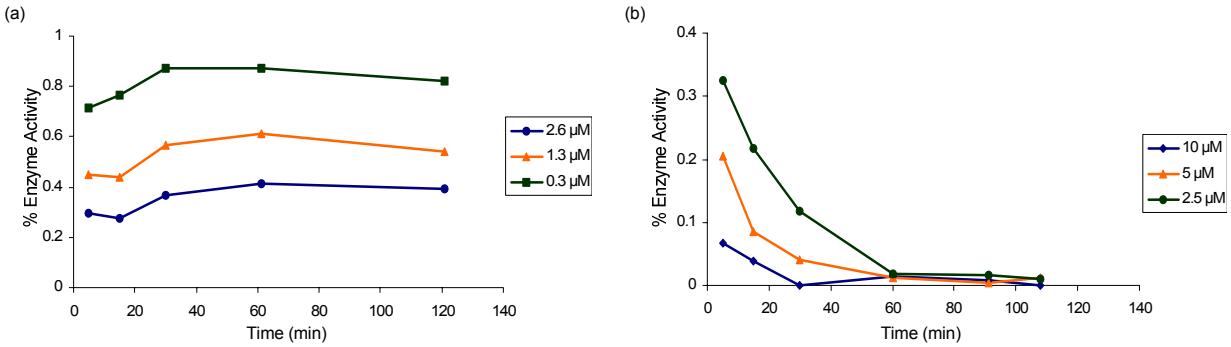


Figure 1.5. Time-dependence of (a) vinyl sulfone **1.45** and (b) β-chloro vinyl sulfone **1.50**.

To gain further insight, we decided to investigate the reversible nature of vinyl sulfone inhibitor **1.45**. Vinyl sulfones are thought to irreversibly alkylate cysteine proteases via a Michael addition followed by protonation of the α-carbon by the active site histidine to form a covalent thioether adduct (Figure 1.6a).[20] Two potential reasons for the reversibility of vinyl sulfone **1.45** are therefore either that the active site cysteine is not adding into the vinyl sulfone or that the active site histidine is not properly oriented for protonating the resulting anion. We postulated that a β–chloro vinyl sulfone could distinguish between these possibilities because cysteine protease inactivation could be accomplished via Michael addition followed by β-

elimination of a chloride ion thereby eliminating the need for anion protonation (Figure 1.6b). Although this particular pharmacophore has never been investigated, it is analogous to previously characterized β–chloro α,β–unsaturated ester inhibitors.[21]

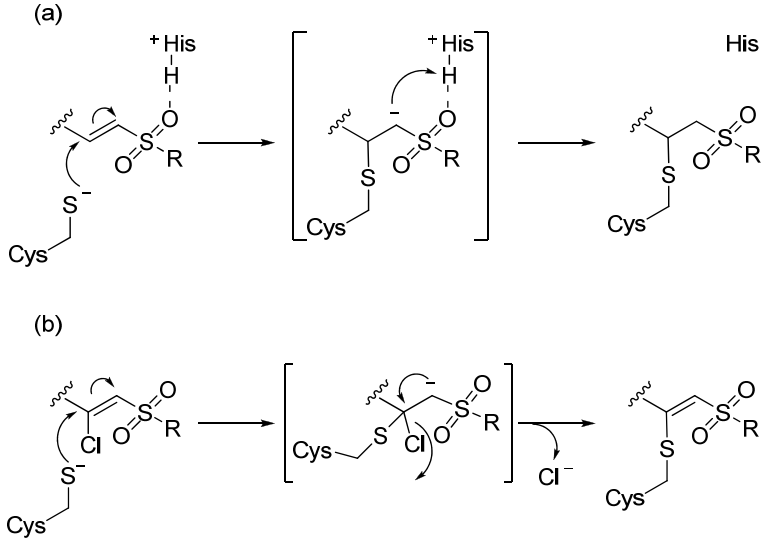


Figure 1.6. Mechanism of inhibition of cysteine proteases by (a) vinyl sulfones and (b) β-chloro vinyl sulfones.

β-Chloro vinyl sulfone inhibitor **1.50** was prepared according to the route depicted in Scheme 1.4 with the key step being conversion of ketosulfone **1.52** to vinyl chloride **1.53** via the vinyl triflate. Gratifyingly, time-dependence analysis and dilution experiments indicated that β-chloro vinyl sulfone inhibitor **1.50** was an irreversible inhibitor of cruzain (Figure 1.5b). This result suggests that the active site cysteine is adding into vinyl sulfone **1.45** and that the lack of a protonation event resulted in a reversible inhibitor. The β-chloro sulfone inhibitor **1.50** had a modest second order rate of inactivation constant of 805 $s^{-1}M^{-1}$ (Table 1.5). Encouraged by this result, we decided to explore other pharmacophores that irreversibly inactivate cysteine proteases according to mechanisms that do not utilize a protonation step.

Scheme 1.4. Synthesis of β-chloro vinyl sulfone inhibitor **1.50**

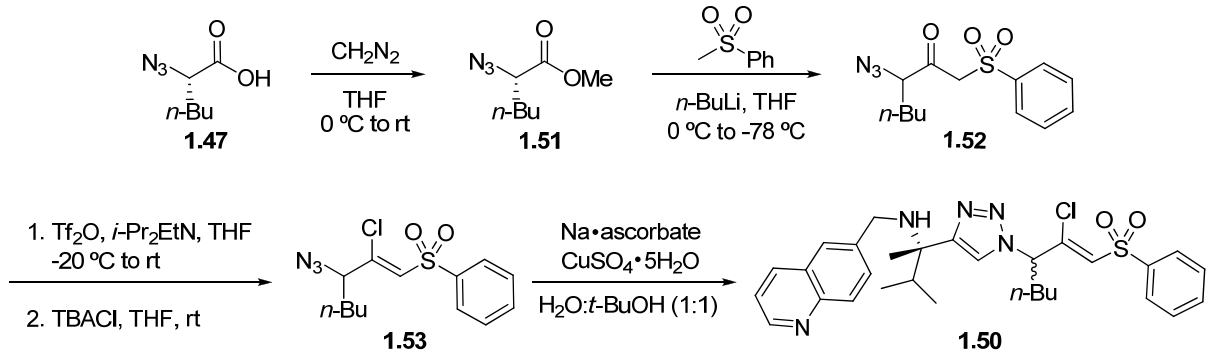
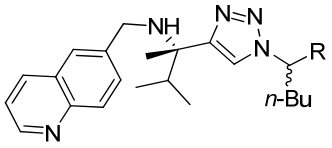
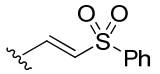
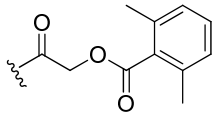
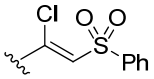
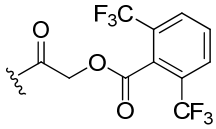
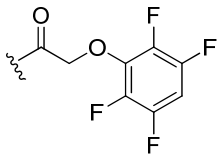


Table 1.5. Second-order inactivation rates of cruzain inhibitors with varying pharmacophores



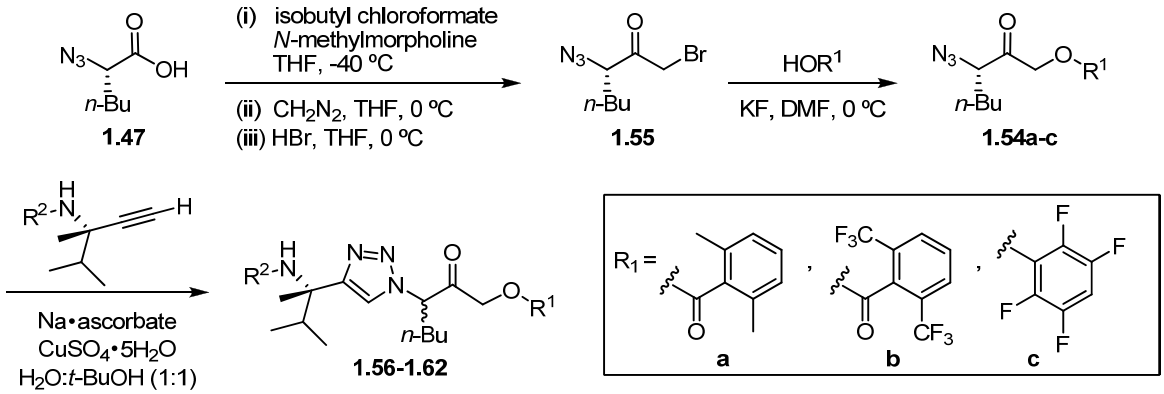
cmpd	R	k_{inact}/K_i ($s^{-1}M^{-1}$)[a]	cmpd	R	k_{inact}/K_i ($s^{-1}M^{-1}$)[a]	pK_a[b]
1.45		-[c]	**1.56**		2,690 ± 334	3.35[d]
1.50		805 ± 144	**1.57**		157,000 ± 1,520	0.58[d]
			1.61		147,000 ± 6,790	>5.5[e]

[a] Tests were performed in quadruplicate (S.D. values included). [b] pK_a of the carboxylic acid or phenol leaving group. [c] No time-dependence observed. [d] Ref 23. [e] Ref 22.

Conversion to Acyl- and Aryl-oxymethyl Ketone Inhibitors

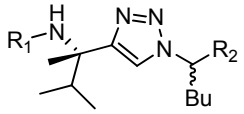
Acyloxymethyl ketone inhibitors were designed by Krantz as more stable halomethyl ketone analogs.[22,23] This pharmacophore has led to potent time-dependent inhibitors of cathepsins B, L, and S.[20] Hence, we next incorporated the acyloxymethyl ketone pharmacophore. The synthesis of the acyloxymethyl ketone inhibitors required the preparation of azide intermediates **1.54a** and **1.54b** (Scheme 1.5). Beginning with L-norleucine azido acid **1.47**, the common bromomethyl ketone precursor **1.55** was obtained in three steps. Displacement of the bromide followed by cyclization with propargyl amine **1.46** then afforded the acyloxymethyl ketone inhibitors **1.56** and **1.57** as mixtures of diastereomers (see Scheme 1.5 and Table 1.5).

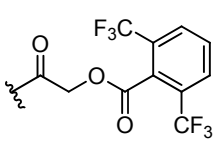
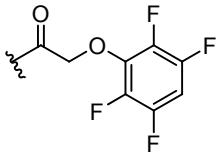
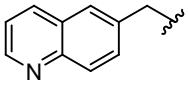
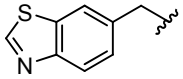
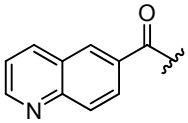
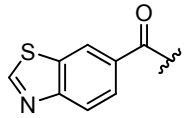
Scheme 1.5. Synthesis of acyl- and aryl-oxymethyl ketone inhibitors



We initially investigated the 2,6-dimethyl acyloxymethyl ketone inhibitor **1.56** and observed that it was an irreversible inhibitor of cruzain with a second-order rate constant of 2,690 $s^{-1}M^{-1}$ (Table 1.5). Acyloxymethyl ketone inhibitors of the cathepsins have shown a strong correlation between the leaving group pK_a and the rate of inactivation.[24] Accordingly, we prepared the 2,6-bis-trifluoromethyl acyloxymethyl ketone inhibitor **1.57** and were delighted to find that inhibitor **1.57** was 58-fold more potent than inhibitor **1.56** with a second-order rate constant of 157,000 $s^{-1}M^{-1}$ (Table 1.5). Inhibitors incorporating this pharmacophore were subsequently prepared corresponding to both the amides and amines of the benzothiazole and quinoline substrates (Scheme 1.5). There was good correlation between substrate activity and inhibitor potency with the amine inhibitors **1.57** and **1.58** being more potent than the amide inhibitors **1.59** and **1.60** (Table 1.6).

Table 1.6. Second-order inactivation rates of 1,2,3-triazole cruzain inhibitors[a]



R_1	R_2 = 	
	**1.57** 157,000 ± 1,520[b]	**1.61** 147,000 ± 6,790[b]
	**1.58** 112,000 ± 5,000[c]	**1.62** 105,000 ± 2,910[c]
	**1.59** 8,730 ± 314[b]	-
	**1.60** 7,550 ± 870[b]	-

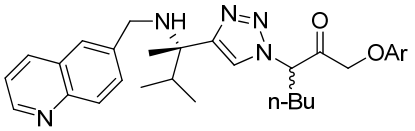
[a] Tests were performed in quadruplicate (S.D. values included). [b] k_{inact}/K_i ($s^{-1}M^{-1}$). [c] k_{ass} ($s^{-1}M^{-1}$).[25]

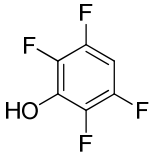
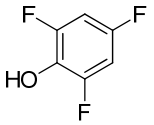
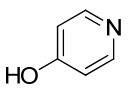
The aryloxymethyl ketone pharmacophore has the same mechanism of inhibition as the acyloxymethyl ketone pharmacophore. It is more attractive, however, because it should be less prone to nucleophilic attack, cannot undergo hydrolysis, and has a lower molecular weight. This pharmacophore has proven to be particularly effective for caspase inhibition.[26,27] In particular, Idun pharmaceuticals used 2,3,5,6-tetrafluorophenol as the leaving group in an aryloxymethyl ketone pan-caspase inhibitor that has progressed to Phase II clinical trials.[28] In contrast, there has only been one report of aryloxymethyl ketone inhibitors of a member of the papain superfamily, and only modest inhibition was observed.[22] Nevertheless, we prepared 2,3,5,6-

tetrafluorophenol aryloxymethyl ketone inhibitor **1.61** (Scheme 1.5). Unexpectedly, the aryloxymethyl ketone inhibitor **1.61** was equipotent to the acyloxymethyl ketone inhibitors with a second-order inactivation constant of 147,000 $s^{-1}M^{-1}$ despite the $>10^5$ difference in the acidity of the corresponding leaving groups (pK_a of 2,3,5,6-tetrafluorophenol > 5.5, pK_a of 2,6-bis-trifluoromethyl benzoic acid = 0.58) (Table 1.5). Inhibitor potency is clearly not solely dependent on the pK_a values of the leaving group with leaving group binding and/or orientation also playing a significant role.[26]

It would be interesting to further explore the aryloxymethyl ketone inhibitor series by varying the phenol leaving group (Table 1.7). Inhibitors with various phenol leaving groups could establish if there is also a correlation between pK_a of the leaving group and inhibitor potency for the aryloxymethyl ketone inhibitor class. By varying the substitution pattern of the fluorine groups, the effect of the binding interactions of these groups would also be probed. The 4-phenoxy-pyridine group is of particular interest as this moiety is equally acidic as the tetrafluorophenoxy group in inhibitor **1.61** but results in an inhibitor with improved pharmacokinetic properties.[29]

Table 1.7. Various aryloxymethyl ketone inhibitors for further exploration



phenol leaving group	pK_a[a]	LogP[b]
	5.5 ± 0.2	6.39
	7.4 ± 0.1	6.07
	7.5 ± 0.2	6.23
	5.2 ± 0.2	4.42

[a] pK_a of the phenol calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994-2008 ACD/Labs). [b] Log P of the inhibitor calculated using ChemDraw v. 11.

Acyl- and Aryl-oxymethyl Ketone Inhibitor Selectivity

To probe the selectivity of the acyl- and aryl-oxymethyl ketone inhibitors for cruzain over the closely related human cathepsins, the four best inhibitors against cruzain were screened against human cathepsin S, K, L, and B (Table 1.8). As might be expected from the modeling studies, the inhibitors were most selective against cathepsin S with 6-fold being the highest selectivity observed. Inhibitor **1.61** was generally the most selective inhibitor with 4- and 5-fold selectivity over cathepsin S and L, respectively. Except for inhibitor **1.61**, the inhibitors were no more than 2-fold selective over cathepsins K and L. Interestingly, the inhibitors were actually more potent against cathepsin B than cruzain. The minimal selectivity for cruzain over the closely related human cathepsins that were investigated is not entirely unexpected as the central domains of these enzymes show high homology.[14,30] Moreover, it has been hypothesized that selectivity over the human enzymes is naturally achieved with cruzain inhibitors due to the differential location of the parasitic versus human proteases. The *T. cruzi* parasite resides in the easily accessible host cell cytoplasm whereas the cathepsins are located in the lysosomes.[6]

Table 1.8. Selectivity profile of inhibitors against cathepsin S, K, L, and B

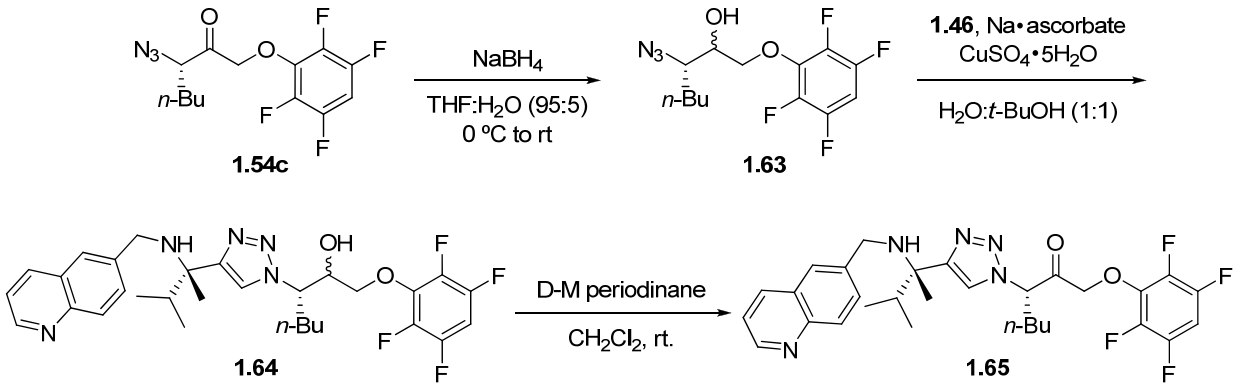
inhibitor	IC_{50} (nM)[a, b] against				
	cruzain	cathepsin S	cathepsin K	cathepsin L	cathepsin B
1.58	11.9 ± 2.6	73.1 ± 14.0	21.3 ± 1.4	14.7 ± 2.6	4.7 ± 1.3
1.60	12.1 ± 2.3	33.5 ± 6.5	24.2 ± 3.1	2.6 ± 0.6	4.2 ± 1.4
1.61	14.3 ± 2.2	56.4 ± 6.0	34.5 ± 5.5	69.3 ± 8.8	7.8 ± 1.4
1.62	13.5 ± 2.1	28.4 ± 5.6	19.1 ± 2.5	16.0 ± 2.9	4.4 ± 2.0

[a] IC_{50} values were determined after 5 minutes of incubation of cruzain and the inhibitor at 37 ºC.
[b] While k_{inact}/K_i values are more accurate for irreversible inhibitors, relative IC_{50} values are relevant as long as they are obtained under the same assay conditions.

Investigation of Configurational Lability of Aryloxymethyl Ketone Inhibitors

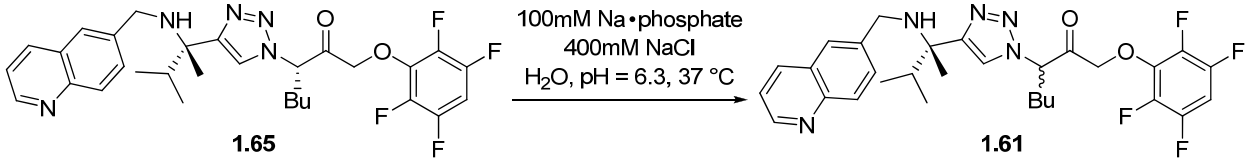
The preparation of both the acyl- and aryl-oxymethyl ketone inhibitors resulted in epimerization alpha to the pharmacophore carbonyl. To investigate the configurational stability of the inhibitors *in vivo*, an alternative sequence for the preparation of diastereomerically pure aryloxymethyl ketone inhibitor **1.61** was developed (Scheme 1.6). Specifically, racemization through enolization was prevented by reducing the acyloxymethyl ketone **1.54c** prior to the cycloaddition step. Alcohol **1.64** was then oxidized back to the acyloxymethyl ketone. The diastereomerically pure inhibitor **1.65** was then subjected to the assay buffer conditions at 37 ºC for several hours (Scheme 1.7). This resulted in complete racemization of the inhibitor within 3 h, suggesting that *in vivo* the inhibitor will be able to funnel through the active diastereomer.

Scheme 1.6. Synthesis of diastereomerically pure aryloxymethyl ketone inhibitor **1.65**



1.54c **1.63** **1.64** **1.65**

Scheme 1.7. Configurational lability of aryloxymethyl ketone inhibitor **1.61**



1.65 **1.61**

Cell Culture Evaluation of Acyl- and Aryl-oxymethyl Ketone Inhibitors

Acyloxymethyl ketone inhibitors **1.57**-**1.60** and aryloxymethyl ketone inhibitors **1.61**-**1.62** were tested for their effectiveness in eliminating *T. cruzi* infection in irradiated (9000 rad) J744 macrophages. Host cells died of *T. cruzi* infection after 5 days without treatment (Table 1.9). Notably, all of the inhibitors significantly delayed *T. cruzi* intracellular replication at concentrations of 5 or 10 μM. The *T. cruzi* infected cells were initially treated with all of the inhibitors at 10 μM concentrations. The cultures treated with each different inhibitor were compared daily by contrast phase microscopy to uninfected macrophage controls. Inhibitors **1.57**, **1.58**, **1.59,** and **1.62** showed toxicity as evidenced by cells that rounded up or detached from the wells, condensed, died, or became granular. For this reason, the concentration of inhibitors **1.57**, **1.58**, **1.59,** and **1.62** was lowered to 5 μM. The 2,6-bis-trifluoromethyl acyloxymethyl ketone inhibitors **1.57**, **1.58**, and **1.59** remained toxic at 5 μM. As a result, it was necessary to stop treatment by day 14 after which point the cells died. Acyloxymethyl ketone inhibitor **1.60** was quite effective at 10 μM in delaying *T. cruzi* replication, however, by day 23 the cell monolayer had been destroyed by the infection.

To distinguish between trypanostatic compounds that only delay parasite replication and trypanocidal compounds that effectively kill *T. cruzi*, treatment for the remaining aryloxymethyl ketone inhibitors was ended on day 27 and the cells were monitored for two more weeks. Benzothiazole aryloxymethyl ketone inhibitor **1.62** proved to be trypanostatic at 5 μM against *T. cruzi* because parasites destroyed the cell monolayer by day 33 (6 days after ending the treatment). Most significantly, the quinoline aryloxymethyl ketone inhibitor **1.61** was trypanocidal at 10 μM and had completely eradicated the *T. cruzi* parasite with no parasites observed at day 40 post-infection. The performance of inhibitor **1.61** was comparable to vinyl sulfone **1.1**, which is the most advanced inhibitor of cruzain to date.

Table 1.9. Effect of inhibitors on survival of *T. cruzi* infected macrophages

cmpd	survival of *T. cruzi* infected cells (days)[a]	last day of treatment (day)	type of inhibition	cell toxicity[e]
none	5	-	-	-
1.1	>40	27[c]	trypanocidal	nontoxic
1.57[b]	30	14[d]	trypanostatic	toxic
1.58[b]	26	14[d]	trypanostatic	toxic
1.59[b]	19	14[d]	trypanostatic	toxic
1.60	23	23	trypanostatic	nontoxic
1.61	>40	27[c]	trypanocidal	nontoxic
1.62[b]	33	27[c]	trypanostatic	nontoxic

[a] Effect of inhibitors on survival of J744 macrophages infected with T. cruzi trypomastigotes, treated daily with a solution of inhibitor (10 μM). Survival time is defined as the time before the cell monolayer is destroyed by the infection.[4] [b] The concentration was lowered to 5 μM after 9 (**1.57**), 7 (**1.58**), and 12 (**1.59**, **1.62**) days. [c] Treatment was ended to distinguish between trypanostatic and trypanocidal inhibitors. [d] Treatment was ended due to compound toxicity. [e] Determined by contrast phase microscopy comparison to uninfected macrophage controls.

Evaluation of Aryloxymethyl Ketone Inhibitors in a Mouse Model of Chagas Disease

Plasma Stability Studies in Mice

Due to the excellent cell culture activity of inhibitor **1.61**, mouse plasma stability studies were performed by ADMETRx as a prelude to the inhibitor's evaluation in animal models of Chagas disease. The inhibitor was incubated at 37 ºC in mouse plasma for 0, 5, 10, 30, or 60 minutes and analyzed by LC/MS for remaining inhibitor. Incubation of the inhibitor with mouse plasma showed no disappearance of the inhibitor with time, indicating it to be 100% stable to mouse plasma under these conditions.

Efficacy Studies in Mice

Mice infected with a large inoculum of *T. cruzi* parasites (1.2 x10^6 trypomastigotes) were treated for 27 days with tetrafluorophenoxymethyl ketone inhibitor **1.61** (Table 1.10). The treatment consisted of 20 mg/kg inhibitor **1.61** in two daily doses via intraperitoneal injection. The mice were monitored for a total of 77 days, at which point they were sacrificed for hemoculture and histopathology. Throughout the experiment, the untreated control mice showed signs of Chagas disease such as ascites (abdominal swelling), malaise, weakness of the hind legs, and ruffled hair. Hemoculture and histopathology revealed that all the untreated mice had positive hemocultures and significant inflammation and infection in heart and skeletal muscle

tissue. The mice treated with inhibitor **1.61**, on the other hand, looked completely normal when sacrificed 77 days post-infection. Importantly, the treatment was well-tolerated by all the mice with no apparent signs of toxicity. Two out of four mice had negative hemocultures, implying animals had no detectable blood parasitemia. Significantly, histopathology revealed that two out of five mice had no inflammation in heart muscle. All the treated mice did show some inflammation in skeletal muscle suggestive of cryptic infection.

The substantial amelioration of acute Chagas disease symptoms is highly significant because, outside of vinyl sulfone **1.1**, there are no other published reports of successful treatment of Chagas disease with inhibitors of cysteine proteases in animal models.[4,31] An alternative treatment regimen with **1.61** or treatment with a more potent analog could lead to a complete cure of *T. cruzi* infected mice. For this reason, a structure-guided design of second-generation inhibitors was carried out (Chapter 2).

Table 1.10. Treatment of *T. cruzi*-infected mice with aryloxymethyl ketone inhibitor **1.61**

group	no. of mice	dose	acute Chagas disease symptoms	no. of mice without *T. cruzi* in tissues[a,b]	no. of mice with negative hemoculture [a,c]
untreated mice	3	none	ascites, paralysis of hind legs, malaise	0	0
treated mice	5	20 mg/kg b.i.d. for 27 days via ip	none	2	2[d]

[a] Mice were sacrificed 77 days post-infection. [b] Tissue analysis of sacrificed animals established the absence/presence of *T. cruzi*. [c] *T. cruzi* was cultured from heart blood collected when animals were sacrificed. [d] Hemocultures were performed for 4/5 mice.

Conclusion

A substrate library containing more than 150 triazole-based substrates developed for cathepsin S was first evaluated against cruzain to define important structural features for efficient substrate cleavage. Subsequent optimization of the substrate scaffold in the S3 pocket was guided by a molecular replacement model and led to nonpeptidic substrates with even greater cleavage efficiency. Vinyl sulfone, β-chloro vinyl sulfone, acyl- and aryl-oxymethyl ketone pharmacophores were then explored in the conversion of the most efficient substrates to inhibitors. The β-chloro vinyl sulfone pharmacophore, which had not previously been reported, led to key mechanistic insight and ultimately resulted in the development of potent irreversible aryloxymethyl ketone inhibitors, a pharmacophore class that had previously been little explored against the papain superfamily.

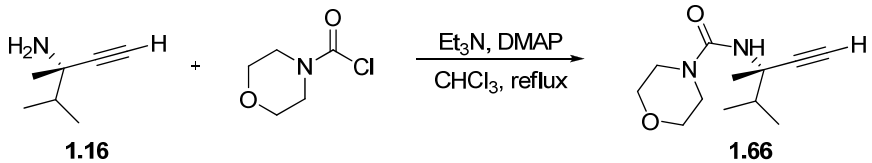
The potent irreversible 2,3,5,6-tetrafluorophenoxymethyl ketone inhibitor **1.61** completely eradicated *T. cruzi* parasites in cell culture. Furthermore, treatment of mice with nonpeptidic inhibitor **1.61** was well-tolerated and resulted in no visible signs of Chagas disease in treated mice. Two mice also had negative hemocultures and displayed no signs of infection in heart tissue. For comparison, a similar treatment regime with the vinyl sulfone inhibitor **1.1**

rescued animals from lethal infection at a higher daily dose (50 mg/kg).[4,31] However, all of the treated mice did show some inflammation in skeletal muscle suggesting unresolved cryptic infection, which has prompted the development of more potent inhibitors. The nonpeptidic nature of this potent class of inhibitors, coupled with their potent cell-based activity and plasma stability, makes these compounds very promising starting points for the development of chemotherapy for Chagas disease.

Experimental Section

General synthetic methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without purification. Tetrahydrofuran (THF), diethyl ether, methylene chloride (CH_2Cl_2), and toluene were obtained from a Seca Solvent Systems by GlassContour (solvent dried over alumina under a N_2 atmosphere). Anhydrous DMF (water <50 ppm) was purchased from Acros. Diisopropylethylamine (*i*-Pr_2EtN) was distilled over CaH_2. Wang resin was purchased from Novabiochem (San Diego, CA), *O*-(7-azabenzothriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) was purchased from PerSeptive Biosystems (Foster City, CA), p-toluenesulfonylmethylnitrosamide (Diazald) was purchased from Sigma-Aldrich. Fmoc-protected 7-amino-4-methyl coumarin acetic acid (Fmoc-AMCA) was synthesized according to a method analogous to the synthesis of 7-amino-4-carbamoylmethylcoumarin (AMC).[32] (*S*)-*tert*-Butanesulfinamide was provided by AllyChem Co. Ltd (Dalian, China). Propargyl amine **1.16** was synthesized as previously reported.[33] Compounds **1.2-1.13**, **1.15**, **1.21, 1.35-1.37**, **1.47, 1.41-1.42** and **1.51** were synthesized as previously reported.[10] All solution-phase reactions were carried out in flame-dried glassware under an inert N_2 atmostphere. Solid-phase reactions were conducted in polypropylene cartridges equipped with 70 mm PE frits (Applied Separations, Allentown, PA) and Teflon stopcocks, and were rocked on an orbital shaker. Reverse-phase HPLC analysis and purification were conducted with an Agilent 1100 series instrument. ^1H, ^{13}C, ^{19}F NMR spectra were obtained on a Bruker AV-300, AVB-400, AVQ-400, or DRX-500 at room temperature. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. ^1H resonances are referenced to $CHCl_3$ (7.26 ppm) or DMSO-d_6 (4.90 ppm), ^{13}C resonances are referenced to $CHCl_3$ (77.23 ppm) or DMSO-d_6 (39.50 ppm), and ^{19}F resonances are referenced to $CFCl_3$ (0 ppm). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer. Melting points were determined on a Laboratory Devices Mel-Temp 3.0 and are reported uncorrected. Elemental analyses and high-resolution mass spectrometry analyses were performed by the University of California at Berkeley Microanalysis and Mass Spectrometry Facilities.

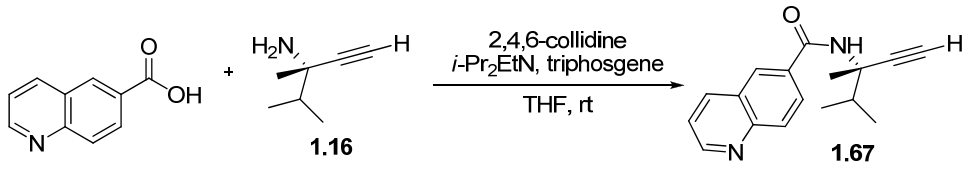
Synthesis of Propargyl Urea and Amide Intermediates



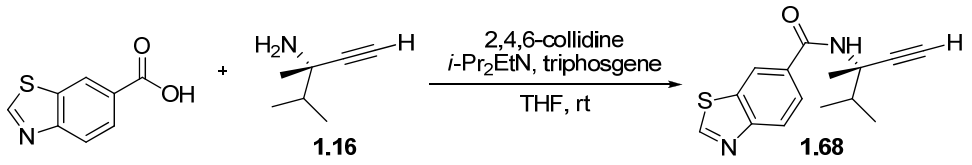
1.16 **1.66**

Propargyl urea 1.66. To a 0.25 M solution of the HCl salt of propargyl amine **1.16** (0.074 g, 0.50 mmol) and triethylamine (0.21 mL, 1.5 mmol) in $CHCl_3$ (2 mL) was added 4-

morpholinecarbonyl chloride (0.082 g, 0.55 mmol). After stirring the resulting solution for 1 h at room temperature, DMAP (0.003 g, 0.02 mmol) was added. The reaction mixture was then stirred at reflux for 2 h. The mixture was washed with saturated aqueous NH_4Cl (1 x 10 mL) and saturated NaCl (1 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (40-60% EtOAc/hexanes) afforded 10.0 mg (8%) of **1.66** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 3H, *J* = 6.9), 1.02 (d, 3H, *J* = 6.9), 1.61 (s, 3H), 2.34 (s, 1H), 2.44 (sept, 1H, *J* = 6.9), 3.31 (t, 4H, *J* = 4.8), 3.68 (t, 4H, *J* = 5.0), 4.54 (br s, 1H). MS (ESI): *m/z* 225 $[MH]^+$.



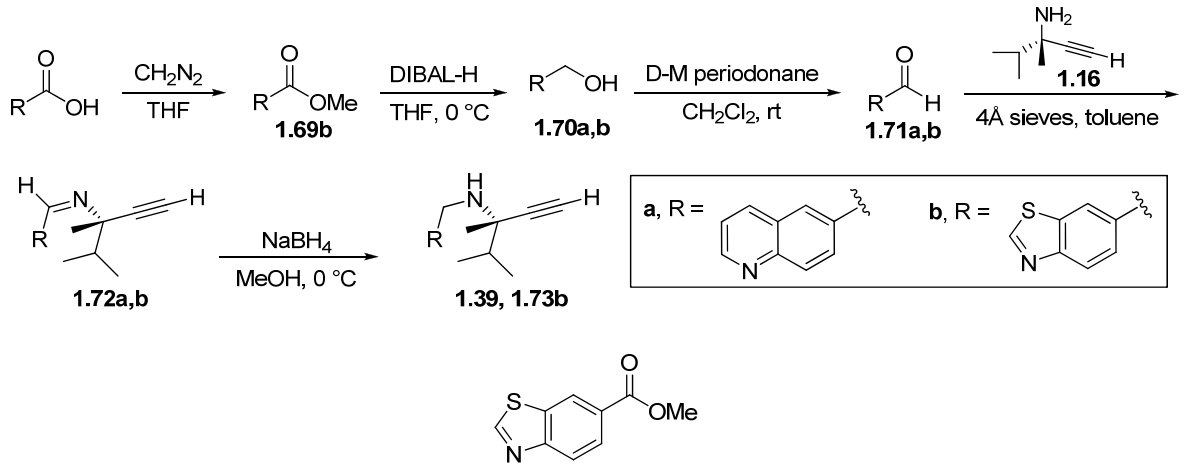
Propargyl amide 1.67. To a 0.17 M solution of the HCl salt of propargyl amine **1.16** (0.050 g, 0.34 mmol) in THF (2 mL) was added *i*-Pr_2EtN (0.472 mL, 2.71 mmol), and to a 0.08 M solution of triphosgene (0.115 g, 0.390 mmol) was added 6-quinolinecarboxylic acid (0.205 g, 1.18 mmol) and 2,4,6-collidine (0.447 mL, 3.39 mmol) in THF (5 mL). The triphosgene mixture was then added to the propargyl amine mixture, and the resulting mixture stirred for 18 h. The reaction mixture was diluted with EtOAc (15 mL) and washed with water (1 x 5 mL), 10% citric acid (2 x 5 mL), and water (3 x 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (30-50% EtOAc/hexanes) afforded 55.0 mg (61%) of **1.67** as an opaque oil. IR ν_{max} (cm^{-1}): 3301, 3051, 2970, 2938, 2877, 2109, 1652. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, 3H, *J* = 6.8), 1.09 (d, 3H, *J* = 6.8), 1.78 (s, 3H), 2.43 (s, 1H), 2.68 (sept, 1H, *J* = 6.8), 6.46 (s, 1H), 7.43 (dd, 1H, *J* = 4.4, 8.4), 7.98 (dd, 1H, *J* = 2.0, 8.8), 8.09 (d, 1H, *J* = 8.8), 8.18 (d, 1H, *J* = 8.4), 8.22 (d, 1H, *J* = 2.0), 8.94 (d, 1H, *J* = 2.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.7, 18.2, 24.3, 34.8, 57.1, 72.0, 84.8, 122.1, 127.2, 127.6, 127.7, 130.1, 133.1, 137.2, 149.4, 152.1, 165.9. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{17}H_{19}N_2O$, 267.1497; found, 267.1499.



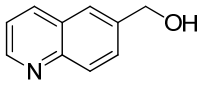
Propargyl amide 1.68. The same procedure as for propargyl amide **1.67** (vide supra) was followed using propargyl amine **1.16** (0.150 g, 1.01 mmol) and *i*-Pr_2EtN (1.41 mL, 8.13 mmol) in THF (6 mL) and triphosgene (0.347 g, 1.17 mmol), 1,3-benzothiazole-6-carboxylic acid (0.647 g, 3.61 mmol), and 2,4,6-collidine (1.34 mL, 10.2 mmol) in THF (15 mL). The reaction was stirred for 24 h. The crude reaction mixture was purified by column chromatography (30-50% EtOAc/hexanes) to afford 0.269 g (98%) of **1.68** as a pale yellow solid. mp 75-76 ºC. IR ν_{max} (cm^{-1}): 3300, 3056, 2970, 2939, 2876, 2110, 1647. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, 3H, *J* = 6.8), 1.09 (d, 3H, *J* = 6.8), 1.77 (s, 3H), 2.43 (s, 1H), 2.67 (sept, 1H, *J* = 6.8), 6.34 (s, 1H), 7.83 (dd, 1H, *J* = 1.6, 8.8), 8.13 (d, 1H, *J* = 8.4), 8.42 (d, 1H, *J* = 1.6), 9.10 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.7, 18.2, 24.4, 34.8, 57.1, 72.0, 84.9, 121.7,

123.7, 124.7, 132.7, 134.3, 155.2, 156.8, 165.8. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{15}H_{17}N_2OS$, 273.1062; found, 273.1057.

Synthesis of Propargyl Amine Intermediates

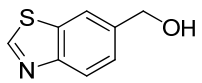


Methyl benzothiazole-6-carboxylate 1.69b. A 0.2 M stirring solution of benzothiazole-6-carboxylic acid in THF (17 mL) was cooled to 0 ºC. Excess diazomethane was introduced *in situ* from Diazald (2.51 g, 11.7 mmol), according to literature procedure.[34] After addition of the diazomethane, the solution was stirred at 0 ºC for 30 min and then at room temperature for 30 min. The solvent was removed under reduced pressure to afford 0.621 g (96%) of **1.69b** as a tan solid. mp 105-106 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (s, 3H), 8.13-8.18 (m, 2H), 4), 7.93 (dd, 1H, J = 0.8, 1.2), 9.14 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 52.6, 123.6, 124.4, 127.5, 127.6, 133.9, 156.2, 157.5, 166.7. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_9H_8NO_2S$, 194.0276; found, 194.0270.

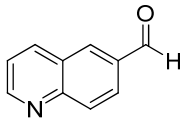


6-Quinolinylmethanol 1.70a. A 0.2 M solution of methyl quinoline-6-carboxylate (0.300 g, 1.60 mmol) in THF (8 mL) and a 0.6 M solution of DIBAL (0.860 mL, 4.81 mmol) in THF (8 mL) were cooled in a -78 ºC acetone-dry ice bath. The DIBAL solution was cannula transferred to the methyl ester solution, and the resulting solution was stirred for 1 h at 0 ºC. The reaction was quenched at 0 ºC by adding methanol (8 mL) and then acetic acid (1.37 mL, 24.0 mmol). After the reaction mixture was stirred for 5 min, a saturated sodium tartrate solution (16 mL) was added. After stirring for 20 min, the reaction mixture was diluted with EtOAc (50 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The organic washes were combined and extracted once with water (15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (50-90% EtOAc/hexanes) afforded 0.236 g (93%) of **1.70a** as a faintly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.89 (s, 2H), 7.35 (dd, 1H, J = 4.0, 8.0), 7.65 (dd, 1H, J = 1.5, 9.0), 7.77 (s, 1H), 8.01 (d, 1H, J = 9.0), 8.08 (d, 1H, J = 4.0), 8.80 (dd, 1H, J = 1.5, 4.0). ^{13}C-NMR (125 MHz,

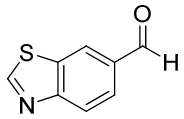
$CDCl_3$): δ 64.8, 121.5, 125.0, 128.3, 129.0, 129.4, 136.4, 139.9, 147.7, 150.2. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{10}H_{10}NO$, 160.0762; found, 160.0766.



(Benzothiazol-6-yl)-methanol 1.70b. The same procedure as for alcohol **1.70a** (vide supra) was followed using methyl benzothiazole-6-carboxylate (0.300 g, 1.55 mmol) in THF (7.75 mL) and DIBAL (0.830 mL, 4.66 mmol) in THF (7.75 mL). The crude reaction mixture was purified by column chromatography (30-50% EtOAc/hexanes) to afford 0.212 g (83%) of **S3b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 2H), 7.37 (dd, 1H, J = 1.2, 8.4), 7.85 (s, 1H), 7.93 (d, 1H, J = 8.4), 8.85 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 64.4, 119.9, 123.2, 125.5, 133.8, 139.3, 152.2, 154.4. HRMS-FAB (m/z): $[MH]^+$ calcd for C_8H_7NOS, 165.0248; found, 165.0243.

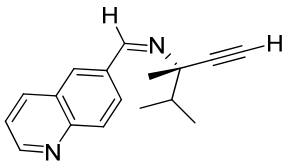


Quinoline-6-carboxyaldehyde 1.71a. This procedure was adapted from Meyers.[35] Dess-Martin periodinane (2.57 g, 6.05 mmol) was added to a 0.28 M solution of 6-quinolinylmethanol (0.459 g, 2.88 mmol) in water-saturated CH_2Cl_2 (10 mL). The reaction mixture was stirred for 10 min and then CH_2Cl_2 (3 x 1 mL) was added over 15 min. The reaction mixture was diluted with diethyl ether (10 mL), and a solution of sodium thiosulfate (7.87 g, 31.7 mmol) in 80% saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was stirred rapidly for 45 min. The layers were separated and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (30 mL), water (2 x 30 mL), and saturated NaCl (2 x 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (30-60% EtOAc/hexanes) to afford 0.383 g (85%) of **1.71a** as a white solid. mp 76.2-76.5 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dd, 1H, J = 4.4, 8.4), 8.18-8.23 (m, 2H), 8.33 (dd, 1H, J = 2.0, 8.4), 8.36 (s, 1H), 9.05 (dd, 1H, J = 2.0, 4.4), 10.20 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 122.4, 126.8, 127.8, 130.9, 133.8, 134.4, 137.6, 151.0, 153.3, 191.6. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{10}H_7NO$, 157.0528; found, 157.0521.

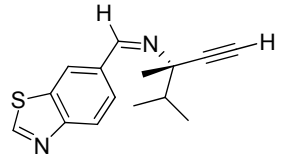


Benzothiazole-6-carboxyaldehyde 1.71b. The same procedure as for aldehyde **1.71a** (vide supra) was followed using **1.70b** (0.175 g, 1.06 mmol), Dess-Martin periodinane (0.943 g, 2.22 mmol) in water-saturated CH_2Cl_2 (3.8 mL). The crude reaction mixture was purified by column chromatography (20-50% EtOAc/hexanes) to afford 0.105 g (61%) of the desired aldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, 1H, J = 1.6, 8.4), 8.24 (d, 1H, J = 8.4), 8.50 (s, 1H), 9.20 (s, 1H), 10.13 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 124.5, 125.2, 127.0, 133.9,

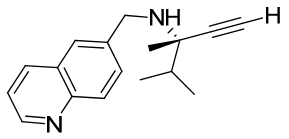
134.6, 157.1, 158.5, 191.4. HRMS-FAB (m/z): $[MH]^+$ calcd for C_8H_5NOS, 163.0092; found, 163.0085.



Propargyl imine 1.72a. The HCl salt of propargyl amine **1.16** (0.248 g, 1.50 mmol) was dissolved in water (1 mL) and basified to pH=11 with 1 M NaOH. The aqueous layer was extracted with toluene (3 x 1.5 mL). The organic layers were combined, dried over Na_2SO_4, and filtered. To the 0.25 M solution of propargyl amine **1.16** in toluene (4.5 mL) were added **1.71a** (0.176 g, 1.12 mmol) and activated 4 Å molecular sieves. The reaction mixture was stirred for 16 h and then filtered through a plug of celite. The celite was washed with CH_2Cl_2 (3 x 5 mL). The organic washes were concentrated to afford 0.237 g (85%) of **1.72a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, 3H, *J* = 6.8), 1.10 (d, 3H, *J* = 6.8), 1.53 (s, 3H), 2.05 (sept, 1H, *J* = 6.8), 2.67 (s, 1H), 7.43 (dd, 1H, *J* = 4.4, 8.4), 8.11-8.13 (m, 2H), 8.21 (d, 1H, *J* = 7.2), 8.28 (dd, 1H, *J* = 2.0, 8.4), 8.83 (s, 1H), 8.94 (dd, 1H, *J* = 2.0, 4.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.0, 18.1, 28.3, 38.3, 66.3, 77.4, 84.1, 121.8, 128.26, 128.29, 129.5, 130.1, 134.9, 136.8, 149.7, 151.4, 157.4. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{17}H_{19}N_2$, 251.1548; found, 251.1543.

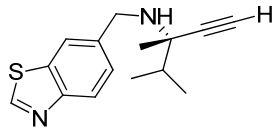


Propargyl imine 1.72b. The same procedure as for propargyl imine **1.72a** (vide supra) was followed using the HCl salt of propargyl amine **1.16** (0.143 g, 0.970 mmol) and benzothiazole-6-carboxyaldehyde (0.105 g, 0.640 mmol) in toluene (2.6 mL) to afford 0.154 g (94%) of **1.72b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, 3H, *J* = 6.8), 1.10 (d, 3H, *J* = 6.8), 1.52 (s, 3H), 2.03 (sept, 1H, *J* = 6.8), 2.68 (s, 1H), 7.97 (dd, 1H, *J* = 1.6, 8.4), 8.16 (d, 1H, *J* = 8.4), 8.39 (d, 1H, *J* = 1.6), 8.78 (s, 1H), 9.03 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.96, 18.01, 28.3, 38.3, 66.2, 77.4, 84.0, 122.2, 123.7, 126.6, 134.2, 134.3, 154.8, 155.7, 157.3. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{15}H_{17}N_2OS$, 257.1112; found, 257.1105.



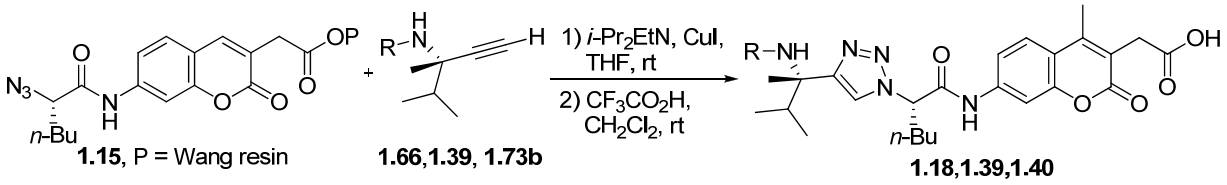
Propargyl Amine 1.46. To a 0.2 M solution of the propargyl imine (0.162 g, 0.700 mmol) in methanol (3.5 mL) at 0 ºC was added sodium borohydride (0.053 g, 1.4 mmol). After stirring the reaction mixture at 0 ºC for 1 h, it was diluted with water (3 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified by column chromatography (30-40% EtOAc/hexanes) to afford 0.122 g (86%) of **1.46** as a white solid. mp 45.9-46.7 ºC. IR ν_{max} (cm^-

[1]): 3299, 2964, 2875, 2360, 2342, 2096. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, 3H, *J* = 6.9), 1.07 (d, 3H, *J* = 6.9), 1.31 (s, 3H), 1.39 (br s, 1H), 1.87 (sept, 1H, *J* = 6.9), 2.39 (s, 1H), 4.00 (d, 1H, *J* = 12.6), 4.06 (d, 1H, *J* = 12.6), 7.36 (dd, 1H, *J* = 4.2, 8.1), 7.74 (dd, 1H, *J* = 1.8, 8.7), 7.78 (s, 1H), 8.05 (d, 1H, *J* = 8.4), 8.11 (dd, 1H, *J* = 1.2, 8.4), 8.86 (dd, 1H, *J* = 1.5, 4.2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.1, 18.1, 23.1, 36.5, 48.3, 57.4, 71.6, 88.0, 121.3, 126.4, 128.4, 129.6, 130.8, 136.0, 139.7, 147.9, 150.2. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{17}H_{21}N_2$, 253.1704; found, 253.1710.

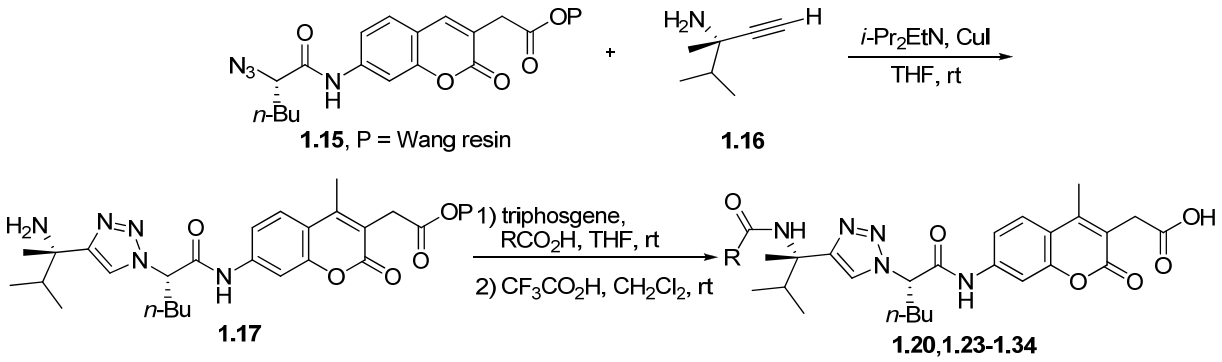


Propargyl amine 1.73b. The same procedure as for propargyl amine **1.46** (vide supra) was followed using **1.72b** (0.154 g, 0.600 mmol) and sodium borohydride (0.045 g, 1.2 mmol) in methanol (3.0 mL). The crude reaction mixture was purified by column chromatography (40-50% EtOAc/hexanes) to afford 0.120 g (77%) of the desired propargyl amine as a pale yellow solid. mp 62.4-63.2 ºC. IR ν_{max} (cm^{-1}): 3291, 3154, 2967, 2086. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (d, 3H, *J* = 6.8), 1.06 (d, 3H, *J* = 6.8), 1.30 (s, 3H), 1.32 (br s, 1H), 1.88 (sept, 1H, *J* = 6.8), 2.38 (s, 1H), 3.97 (d, 1H, *J* = 12.4), 4.02 (d, 1H, *J* = 12.4), 7.52 (dd, 1H, *J* = 1.6, 8.4), 7.98 (d, 1H, *J* = 0.8), 8.06 (d, 1H, *J* = 8.4), 8.94 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.0, 18.1, 23.1, 36.5, 48.3, 57.4, 71.6, 87.9, 121.3, 123.5, 127.2, 134.0, 139.1, 152.5, 153.8. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{15}H_{19}N_2S$, 259.1269; found, 259.1270.

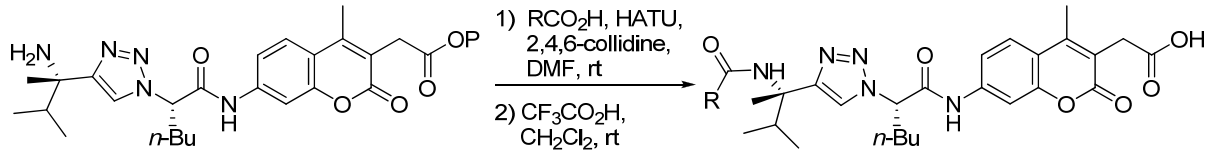
General Procedures for the Synthesis of Aminocoumarin Substrates



General synthesis of urea substrate 18 and amine substrates 1.39-1.40 (Procedure A). To resin **1.15** (0.35-0.65 mmol/g, 1 equiv), preswollen in THF, was added a 0.02 M solution of a propargylamine intermediate (1-2.2 equiv) and *i*-Pr_2EtN (100 equiv) in THF. CuI (3 equiv) was then added and the mixture was shaken for 48 h. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, CH_3CN, THF, and CH_2Cl_2, and then the product was cleaved from support and purified following Procedure D (vide infra).



General synthesis of amide substrates 1.20 and 1.23-1.34 (Procedure B). To resin **1.15** (0.115 g, 0.0750 mmol), preswollen in THF, was added a 0.02 M solution of the HCl salt of propargylamine **1.16** (0.025 g, 0.17 mmol) and *i*-Pr_2EtN (1.3 mL, 7.5 mmol) in THF (8.2 mL). CuI (0.043 g, 0.23 mmol) was then added and the mixture was shaken for 48 h. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, CH_3CN, and THF to afford support-bound amine intermediate **1.17**. After washing derivatized resin **1.17**, *i*-Pr_2EtN (8 equiv) was added. To a 0.1 M solution of carboxylic acid (3.3-3.5 equiv) in THF with triphosgene (1.1 equiv) was added 2,4,6-collidine (10 equiv). The resulting slurry was stirred for about 1 min and was then added to the cartridge containing resin **1.17**. The resulting mixture was shaken for 4-12 h. After removal of the solution, the resin was washed with THF (20 mL) and the coupling was repeated two more times. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, THF, and CH_2Cl_2, and then the product was cleaved from support and purified following Procedure D (vide infra).

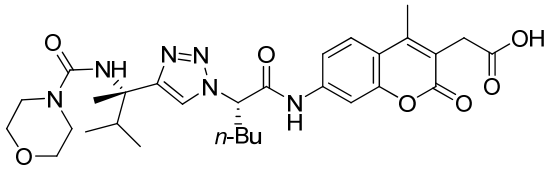


General synthesis of amide substrates 1.19, 1.22, and 1.29 (Procedure C). To resin **1.15** (0.115 g, 0.0750 mmol), preswollen in THF, was added a 0.02 M solution of the HCl salt of propargylamine **1.16** (0.025 g, 0.17 mmol) and *i*-Pr_2EtN (1.3 mL, 7.5 mmol) in THF (8.2 mL). CuI (0.043 g, 0.23 mmol) was then added, and the mixture was shaken for 48 h. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, CH_3CN, and THF to afford support-bound amine intermediate **1.17**. Resin **1.17** was swollen with three portions (20 mL) of DMF. A 0.4 M solution of HATU (5.0-7.0 equiv), 2,4,6-collidine (5.0-7.0 equiv), and the carboxylic acid (5.0-7.0 equiv) in DMF was added to the resin, and the mixture was shaken for 48 h. After removal of the solution, the resin was washed with three portions (20 mL) each of DMF, THF, CH_3OH, THF, and CH_2Cl_2, and then the product was cleaved from support and purified following Procedure D (vide infra).

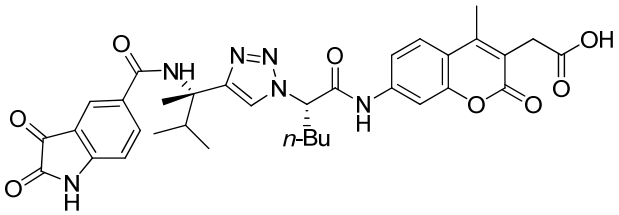
General procedure for support cleavage and purification of substrates (Procedure D). The resin was swollen in CH_2Cl_2. To the swollen resin was added a solution of 9:1 CH_2Cl_2:(95% CF_3CO_2H, 2.5% H_2O, 2.5% triisopropylsilane), and the mixture was shaken 1 h.

Upon removal of the solution, the resin was washed with one portion of the cleavage solution (5 mL) and three portions of CH_2Cl_2 (5 mL). The combined washes were concentrated under reduced pressure. The crude product mixture was purified by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to 95:5 over 55 min; 10mL/min; 254 nm detection for 65 min] and lyophilized. The purity of each compound was confirmed by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in two solvent systems: CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min; CH_3OH/H_2O, 5:95 to 95:5 over 20 min, 95:5 for 10 min).

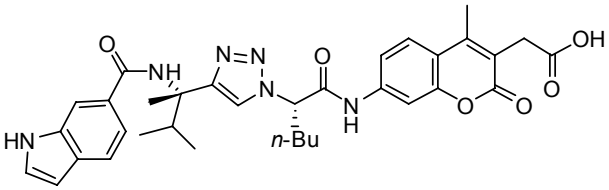
Synthesis of Aminocoumarin Substrates



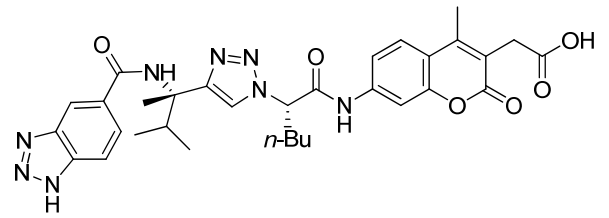
Urea substrate 1.18. Procedure A was followed using resin **1.15** (0.136 g, 0.0890 mmol), propargyl urea **1.66** (0.010 g, 0.044 mmol), *i*-Pr_2EtN (1.6 mL, 8.9 mmol), and CuI (0.050 g, 0.27 mmol) in THF (2.2 mL) to afford 8.4 mg (32%) of **1.18** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.63 (d, 3H, *J* = 6.8), 0.81-0.85 (m, 6H), 1.05-1.35 (m, 4H), 1.60 (s, 3H), 2.10-2.23 (m, 2H), 2.37 (s, 3H), 2.51 (overlap with solvent), 3.15-3.24 (m, 4H), 3.48-3.55 (M, 4H), 3.58 (s, 2H), 5.43 (dd, 1H, *J* = 6.6, 8.6), 6.20 (s, 1H), 7.49 (dd, 1H, *J* = 1.6, 8.8), 7.73 (d, 1H, *J* = 1.6), 7.81 (d, 1H, *J* = 8.8), 8.03 (s, 1H), 10.95 (s, 1H), 12.40 (br s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{30}H_{40}N_6O_7Na$, 619.2856; found, 619.2855.



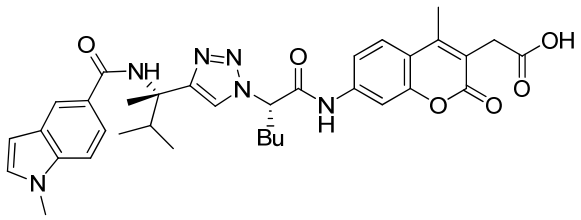
Amide substrate 1.19. Procedure C was followed using 5-carboxy-indole (0.093 g, 0.525 mmol), HATU (0.200 g, 0.525 mmol), and 2,4,6-collidine (0.069 mL, 0.525 mmol) in DMF (1.3 mL) to afford 7.0 mg (14%) of **1.19** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.72 (d, 3H, *J* = 6.4), 0.83 (t, 3H, *J* = 7.2), 0.90 (d, 3H, *J* = 6.4), 1.01-1.38 (m, 4H), 1.71 (s, 3H), 2.07-2.24 (m, 2H), 2.36 (s, 3H), 2.66 (sept, 1H, *J* = 7.2), 3.58 (s, 2H), 5.36-5.48 (m, 1H), 6.94 (d, 1H, *J* = 8.0), 7.49 (d, 1H, *J* = 8.0), 7.72 (s, 1H), 7.80 (d, 1H, *J* = 8.8), 7.89-8.15 (m, 4H), 10.94 (s, 1H), 11.41 (s, 1H), 12.42 (br s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{34}H_{37}N_6O_8$, 657.2673; found, 657.2661.



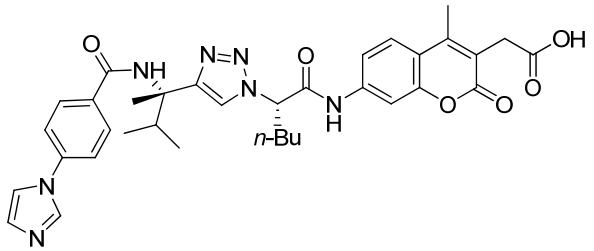
Amide substrate 1.20. Procedure B was followed using indole-6-carboxylic acid (0.042 g, 0.075 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 7.0 mg (15%) of **1.20** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.71 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.4), 0.91 (d, 3H, *J* = 6.8), 1.05-1.37 (m, 4H), 1.78 (s, 3H), 2.13-2.24 (m, 2H), 2.36 (s, 3H), 2.72 (sept, 1H, *J* = 6.8), 3.58 (s, 2H), 5.46 (dd, 1H, *J* = 7.2, 8.8), 6.47 (s, 1H), 7.42 (d, 1H, *J* = 8.4), 7.47-7.52 (m, 2H), 7.56 (d, 1H, *J* = 8.4), 7.72 (d, 1H, *J* = 2.0), 7.80 (d, 1H, *J* = 8.8), 7.86 (s, 1H), 7.94 (s, 1H), 8.17 (s, 1H), 10.96 (s, 1H), 11.34 (s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{34}H_{38}N_6O_6Na$, 649.2751; found, 649.2744.



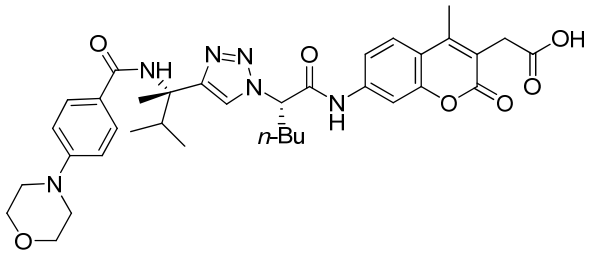
Amide substrate 1.22. Procedure C was followed using benzotriazole-5-carboxylic acid (0.086 g, 0.53 mmol), HATU (0.200 g, 0.525 mmol), and 2,4,6-collidine (0.069 mL, 0.525 mmol) in DMF (1.3 mL) to afford 7.9 mg (17%) of **1.22** as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.74 (d, 3H, *J* = 6.5), 0.83 (t, 3H, *J* = 7.2), 0.93 (d, 3H, *J* = 6.5), 1.05-1.38 (m, 4H), 1.76 (s, 3H), 2.14-2.22 (m, 2H), 2.36 (s, 3H), 2.68 (sept, 1H, *J* = 6.5), 3.58 (s, 2H), 5.45 (dd, 1H, *J* = 7.5, 8.0), 7.49 (d, 1H, *J* = 8.5), 7.72 (s, 1H), 7.79-7.82 (m, 2H), 7.90 (br s, 1H), 8.16 (s, 1H), 8.25 (s, 1H), 8.40 (br s, 1H), 10.96 (s, 1H), 12.38 (br s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{32}H_{36}N_8O_6Na$, 651.2656; found, 651.2660.



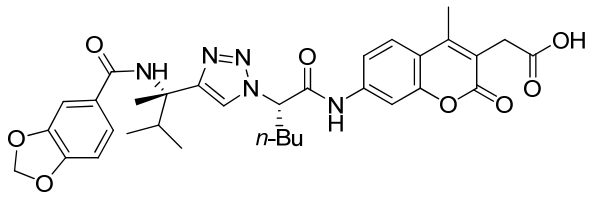
Amide substrate 1.23. Procedure B was followed using 1-methyl-1*H*-indole-5-carboxylic acid (0.037 g, 0.060 mmol), triphosgene (0.020 g, 0.07 mmol), 2,4,6-collidine (0.080 mL, 0.60 mmol), and *i*-Pr_2EtN (0.09 mL, 0.48 mmol) to afford 2.3 mg (6%) of **1.23** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.71 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.91 (d, 3H, *J* = 6.8), 1.05-1.37 (m, 4H), 1.78 (s, 3H), 2.12-2.24 (m, 2H), 2.36 (s, 3H), 2.73 (sept, 1H, *J* = 6.8), 3.58 (s, 2H), 3.80 (s, 3H), 5.43-5.51 (m, 1H), 6.53 (d, 1H, *J* = 3.2), 7.39 (d, 1H, *J* = 2.8), 7.45 (d, 1H, *J* = 8.8), 7.49 (d, 1H, *J* = 8.8), 7.58 (d, 1H, *J* = 8.8), 7.72 (d, 1H, *J* = 2.0), 7.79 (d, 1H, *J* = 8.8), 7.90 (s, 1H), 8.05 (s, 1H), 8.15 (s, 1H), 10.96 (s, 1H), 12.51 (br s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{35}H_{40}N_6O_6Na$, 663.2907; found, 663.2910.



Amide substrate 1.24. Procedure B was followed using 4-(1*H*-imidazol-1-yl)-benzoic acid (0.049 g, 0.26 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 18.4 mg (38%) of **1.24** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.92 (d, 3H, *J* = 6.8), 1.10-1.38 (m, 4H), 1.75 (s, 3H), 2.14-2.23 (m, 2H), 2.36 (s, 3H), 2.67 (sept, 1H, *J* = 6.8), 3.58 (s, 2H), 5.45 (dd, 1H, *J* = 6.8, 8.4), 7.47 (dd, 1H, *J* = 2.0, 8.8), 7.75 (d, 1H, *J* = 2.0), 7.79-7.89 (m, 4H), 8.00 (d, 2H, *J* = 8.4), 8.16 (s, 1H), 8.24 (s, 1H), 8.32 (br s, 1H), 9.62 (br s, 1H), 11.00 (s, 1H), 12.47 (br s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{35}H_{40}N_7O_6$, 654.3040; found, 654.3035.

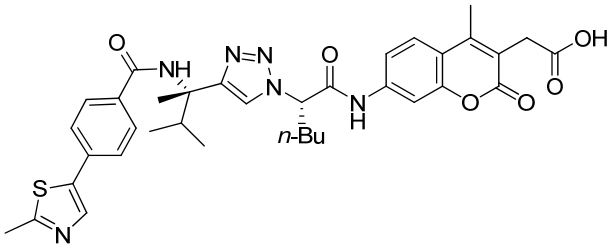


Amide substrate 1.25. Procedure B was followed using 4-morpholinobenzoic acid (0.050 g, 0.24 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 31.4 mg (62%) of **1.25** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.68 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.88 (d, 3H, *J* = 6.8), 1.10-1.37 (m, 4H), 1.72 (s, 3H), 2.12-2.23 (m, 2H), 2.36 (s, 3H), 2.68 (sept, 1H, *J* = 6.8), 3.15-3.21 (m, 4H), 3.57 (s, 2H), 3.69-3.75 (m, 4H), 5.44 (dd, 1H, *J* = 6.8, 8.6), 6.94 (d, 2H, *J* = 8.8), 7.49 (dd, 1H, *J* = 2.0, 8.8), 7.67 (d, 2H, *J* = 8.8), 7.72 (d, 1H, *J* = 2.0), 7.75 (s, 1H), 7.80 (d, 1H, *J* = 8.8), 8.12 (s, 1H), 10.95 (s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{36}H_{44}N_6O_7Na$, 688.2417; found, 688.2411.

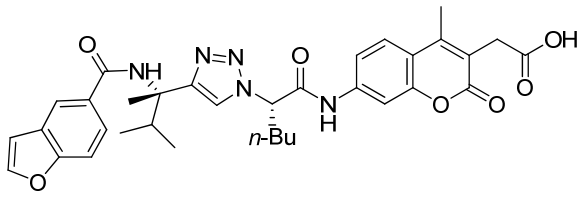


Amide substrate 1.26. Procedure B was followed using piperonylic acid (0.043 g, 0.26 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 24.2 mg (51%) of **1.26** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.70 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.88 (d, 3H, *J* = 6.8), 1.10-1.36 (m, 4H),

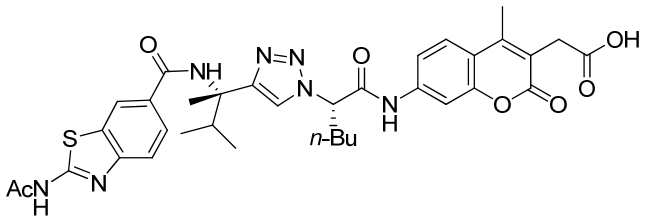
1.71 (s, 3H), 2.13-2.22 (m, 2H), 2.36 (s, 3H), 2.65 (sept, 1H, J = 6.8), 3.58 (s, 2H), 5.44 (dd, 1H, J = 6.6, 8.8), 6.07 (s, 2H), 6.96 (d, 1H, J = 8.0), 7.30 (d, 1H, J = 1.2), 7.34-7.37 (m, 1H), 7.49 (dd, 1H, J = 2.0, 8.8), 7.72 (d, 1H, J = 2.0), 7.80 (d, 1H, J = 8.8), 7.86 (s, 1H), 8.11 (s, 1H), 10.95 (s, 1H), 12.50 (br s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{33}H_{37}N_5O_8Na$, 654.2540; found, 654.2529.



Amide substrate 1.27. Procedure B was followed using 4-(2-methyl-4-thiazolyl)benzoic acid (0.046 g, 0.060 mmol), triphosgene (0.020 g, 0.070 mmol), 2,4,6-collidine (0.080 mL, 0.60 mmol), and *i*-Pr_2EtN (0.090 mL, 0.48 mmol) to afford 8.2 mg (20%) of **1.27** as a white powder. ^1H NMR (500 MHz, DMSO-d_6): δ 0.72 (d, 3H, J = 6.8), 0.83 (t, 3H, J = 7.5), 0.91 (d, 3H, J = 6.5), 1.05-1.37 (m, 4H), 1.74 (s, 3H), 2.13-2.23 (m, 2H), 2.36 (s, 3H), 2.65-2.73 (m, 4H), 3.58 (s, 2H), 5.42-5.48 (m, 1H), 7.50 (d, 1H, J = 8.5), 7.73 (s, 1H), 7.77-7.86 (m, 3H), 7.99 (d, 2H, J = 8.0), 8.06 (d, 2H, J = 7.0), 8.15 (s, 1H), 10.97 (s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{36}H_{41}N_6O_6S$, 685.2808; found, 685.2798.

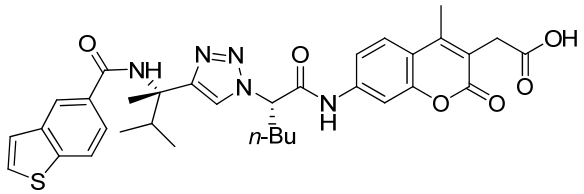


Amide substrate 1.28. Procedure B was followed using 1-benzofuran-5-carboxylic acid (0.041 g, 0.25 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 21.9 mg (47%) of **1.28** as a white powder. ^1H NMR (400 MHz, DMSO-d_6): δ 0.73 (d, 3H, J = 6.8), 0.83 (t, 3H, J = 7.2), 0.92 (d, 3H, J = 6.8), 1.06-1.38 (m, 4H), 1.75 (s, 3H), 2.13-2.22 (m, 2H), 2.36 (s, 3H), 2.69 (sept, 1H, J = 6.8), 3.58 (s, 2H), 5.41-5.50 (m, 1H), 7.06 (d, 1H, J = 2.0), 7.50 (dd, 1H, J = 2.0, 8.8), 7.63 (d, 1H, J = 8.6), 7.70-7.75 (m, 2H), 7.80 (d, 1H, J = 8.6), 8.04-8.08 (m, 2H), 8.09-8.12 (m, 1H), 8.15 (s, 1H), 10.95 (s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{34}H_{37}N_5O_7Na$, 650.2591; found, 650.2587.

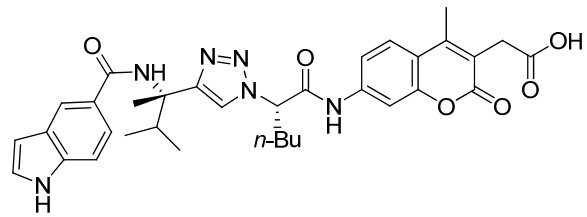


Amide substrate 1.29. To a 0.6 M solution of 2-aminobenzothiazole-6-carboxylic acid hydrochloride[36] (0.500 g, 2.17 mmol) in CH_2Cl_2 (3.6 mL) was added TMS-Cl (0.61 mL, 4.7

mmol) and *i*-Pr_2EtN (1.50 mL, 8.67 mmol). The reaction mixture was heated at reflux for 3 h. After cooling the mixture to 0 ˚C, FmocCl (0.617 g, 2.38 mmol) was added slowly. The reaction mixture was stirred for 15 h at room temperature. MeOH (13 mL) was added with rapid stirring until a white precipitate formed. The precipitate was filtered and washed with MeOH (7 mL) and Et_2O (7 mL). Procedure C was then followed using the crude Fmoc-protected carboxylic acid (0.16 g, 0.038 mmol), HATU (0.14 g, 0.038 mmol), and 2,4,6-collidine (0.05 mL, 0.038 mmol) in DMF (1 mL). After washing the resin according to Procedure C, it was subjected to a solution of 20% piperidine in DMF (5 mL) for 5 min. The resin was rinsed with DMF (5 mL) and resubjected to a solution of 20% piperidine in DMF for 5 min. After removal of the solution, the resin was washed with three portions (20 mL) each of DMF and CH_2Cl_2. To a solution of DMAP (1 mg, 0.008 mmol) in CH_2Cl_2 (1 mL) was added *i*-Pr_2EtN (0.039 mL, 0.22 mmol) and acetic anhydride (0.033 mL, 0.34 mmol). The resulting acylating solution was then added to the cartridge containing the resin. The resulting mixture was shaken for 19 h. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, THF, and CH_2Cl_2, and then the product was cleaved from support and purified following Procedure D to afford 5.9 mg (11%) of **1.29** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.74 (d, 3H, *J* = 6.8), 0.84 (t, 3H, *J* = 7.2), 0.93 (d, 3H, *J* = 6.8), 1.04-1.39 (m, 4H), 1.76 (s, 3H), 2.13-2.26 (m, 2H), 2.22 (s, 3H), 2.37 (s, 3H), 2.70 (sept, 1H, *J* = 6.8), 3.59 (s, 2H), 5.41-5.48 (m, 1H), 7.51 (d, 1H, *J* = 8.4), 7.72-7.84 (m, 5H), 8.07 (s, 1H), 8.15 (s, 1H), 8.41 (s, 1H), 10.95 (s, 1H), 12.48 (br s, 1H). MS (ESI): *m/z* 702 $[MH]^+$.

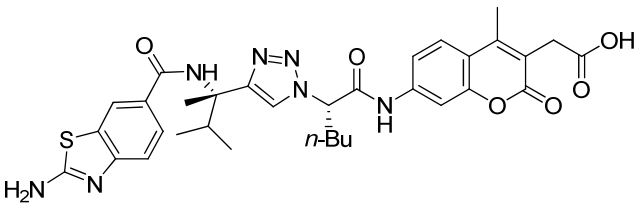


Amide substrate 1.30. Procedure B was followed using 1-benzothiaphene-5-carboxylic acid (0.038 g, 0.060 mmol), triphosgene (0.020 g, 0.070 mmol), 2,4,6-collidine (0.080 mL, 0.60 mmol), and *i*-Pr_2EtN (0.09 mL, 0.48 mmol) to afford 10.9 mg (28%) of **1.30** as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.74 (d, 3H, *J* = 6.5), 0.83 (t, 3H, *J* = 7.0), 0.93 (d, 3H, *J* = 6.5), 1.02-1.37 (m, 4H), 1.76 (s, 3H), 2.13-2.24 (m, 2H), 2.36 (s, 3H), 2.70 (sept, 1H, *J* = 6.5), 3.58 (s, 2H), 5.41-5.50 (m, 1H), 7.50 (d, 1H, *J* = 8.5), 7.56 (d, 1H, *J* = 5.5), 7.19-7.27 (m, 2H), 7.79 (d, 1H, *J* = 9.0), 7.83 (d, 1H, *J* = 5.5), 8.05 (d, 1H, *J* = 8.5), 8.12 (s, 1H), 8.16 (s, 1H), 8.31 (s, 1H), 10.97 (s, 1H), 12.53 (br s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{34}H_{38}N_5O_6S$, 644.2543; found, 649.2553.

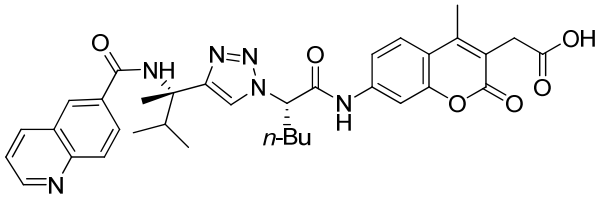


Amide substrate 1.31. Procedure B was followed using indole-5-carboxylic acid (0.041 g, 0.25 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-

Pr_2EtN (0.11 mL, 0.60 mmol) to afford 2.0 mg (4%) of **1.31** as a white powder. ^1H NMR (400 MHz, DMSO-d_6): δ 0.71 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.91 (d, 3H, *J* = 6.8), 1.08-1.37 (m, 4H), 1.76 (s, 3H), 2.13-2.25 (m, 2H), 2.36 (s, 3H), 2.72 (sept, 1H, *J* = 6.8), 3.58 (s, 2H), 5.40-5.49 (m, 1H), 6.51-6.54 (m, 1H), 7.38-7.43 (m, 2H), 7.47-7.56 (m, 2H), 7.72 (d, 1H, *J* = 2.0), 7.79 (d, 1H, *J* = 8.8), 7.88 (s, 1H), 8.05 (s, 1H), 8.16 (s, 1H), 10.97 (s, 1H), 11.30 (s, 1H), 12.46 (br s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{34}H_{38}N_6O_6Na$, 649.2751; found, 649.2748.

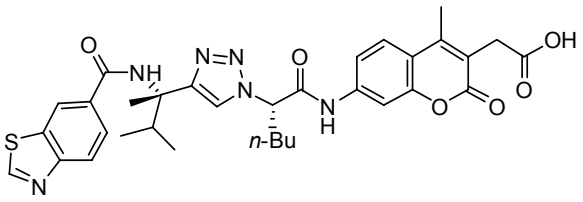


Amide substrate 1.32. To a 0.6 M solution of 2-aminobenzothiazole-6-carboxylic acid hydrochloride[36] (0.500 g, 2.17 mmol) in CH_2Cl_2 (3.6 mL) was added TMS-Cl (0.61 mL, 4.7 mmol) and *i*-Pr_2EtN (1.50 mL, 8.67 mmol). The reaction mixture was heated at reflux for 3 h. After cooling the mixture to 0 ˚C, FmocCl (0.617 g, 2.38 mmol) was added slowly. The reaction mixture was stirred for 15 h at room temperature. MeOH (13 mL) was added with rapid stirring until a white precipitate formed. The precipitate was filtered and washed with MeOH (7 mL) and Et_2O (7 mL). Procedure B was then followed using the crude Fmoc-protected carboxylic acid (0.103 g, 0.25 mmol), triphosgene (0.025 g, 0.08 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 11.4 mg (17%) of Fmoc-**1.32**. The substrate was then deprotected by subjecting it to a solution of 20% piperidine in DMF (1 mL) for 15 min. The solution was concentrated under reduced pressure, purified by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to 95:5 over 55 min; 10mL/min; 254 nm detection for 65 min], and lyophilized to afford 3.2 mg (38%) of **1.32** as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 0.71 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.90 (d, 3H, *J* = 6.8), 1.05-1.35 (m, 4H), 1.73 (s, 3H), 2.12-2.23 (m, 2H), 2.36 (s, 3H), 2.68 (sept, 1H, *J* = 6.8), 3.58 (s, 2H), 5.41-5.48 (m, 1H), 7.35 (s, 1H), 7.49 (dd, 1H, *J* = 2.0, 8.8), 7.66 (dd, 1H, *J* = 1.6, 8.4), 7.72 (d, 1H, *J* = 2.0), 7.80 (d, 1H, *J* = 8.8), 7.92 (s, 1H), 8.01 (br s, 2H), 8.13 (s, 2H), 10.97 (s, 1H), 12.45 (br s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{33}H_{37}N_7O_6SNa$, 682.2424; found, 682.2424.

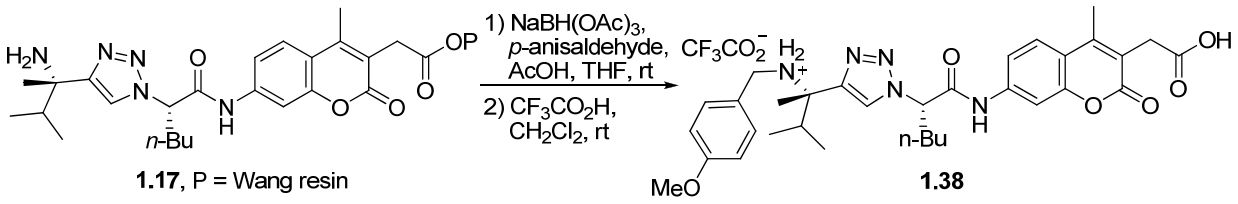


Amide substrate 1.33. Procedure B was followed using 6-quinolinecarboxylic acid (0.045 g, 0.26 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 18.0 mg (38%) of **1.33** as a white powder. ^1H NMR (500 MHz, DMSO-d_6): δ 0.76 (d, 3H, *J* = 6.8), 0.83 (t, 3H, *J* = 7.2), 0.95 (d, 3H, *J* = 6.8), 1.05-1.37 (m, 4H), 1.78 (s, 3H), 2.12-2.23 (m, 2H), 2.35 (s, 3H), 2.71 (sept, 1H, *J* = 6.8), 3.57 (s, 2H), 5.41-5.49 (m, 1H), 7.48 (d, 1H, *J* = 9.0), 7.68-7.76 (m, 2H), 7.78 (d, 1H, *J* = 8.5), 8.07-8.16

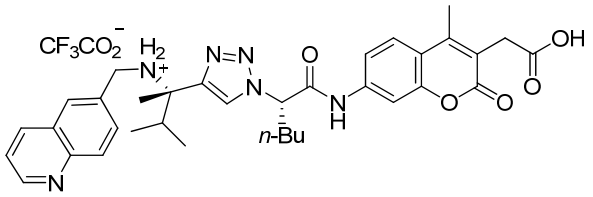
(m, 2H), 8.18 (s, 1H), 8.36 (s, 1H), 8.51 (s, 1H), 8.67 (d, 1H, J = 8.5), 9.06 (m, 1H), 10.98 (s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{35}H_{39}N_6O_6$, 639.2931; found, 639.2918.



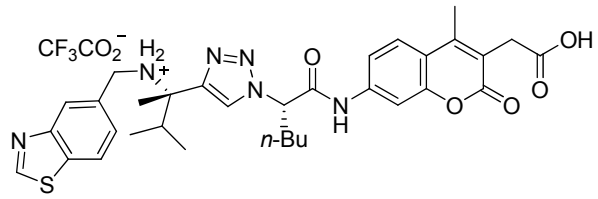
Amide substrate 1.34. Procedure B was followed using 1,3-benzothiazole-6-carboxylic acid (0.044 g, 0.25 mmol), triphosgene (0.025 g, 0.080 mmol), 2,4,6-collidine (0.10 mL, 0.75 mmol), and *i*-Pr_2EtN (0.11 mL, 0.60 mmol) to afford 18.0 mg (37%) of **1.34** as a white powder. ^1H NMR (500 MHz, DMSO-d_6): δ 0.74 (d, 3H, J = 7.0), 0.82 (t, 3H, J = 7.2), 0.93 (d, 3H, J = 7.0), 1.05-1.37 (m, 4H), 1.76 (s, 3H), 2.12-2.24 (m, 2H), 2.35 (s, 3H), 2.67 (sept, 1H, J = 7.0), 3.58 (s, 2H), 5.45 (dd, 1H, J = 6.5, 8.5), 7.49 (dd, 1H, J = 2.0, 9.0), 7.72 (d, 1H, J = 2.0), 7.79 (d, 1H, J = 9.0), 7.90 (dd, 1H, J = 2.0, 8.5), 8.11 (d, 1H, J = 8.5), 8.16 (s, 1H), 8.20 (s, 1H), 8.59 (d, 1H, J = 1.0), 9.50 (s, 1H), 10.97 (s, 1H). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{33}H_{36}N_6O_6SNa$, 667.2315; found, 667.2322.



Amine substrate 1.38. To resin **1.15** (0.115 g, 0.0750 mmol), preswollen in THF, was added a 0.02 M solution of the HCl salt of propargylamine **1.16** (0.025 g, 0.17 mmol) and *i*-Pr_2EtN (1.3 mL, 7.5 mmol) in THF (8.2 mL). CuI (0.043 g, 0.23 mmol) was then added and the mixture was shaken for 48 h. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, CH_3CN, and THF to afford support-bound amine intermediate **1.17**. After washing derivatized resin **1.17**, THF (2.0 mL, 0.8 M) was added. To this solution was added *p*-anisaldehyde (0.102 g, 0.750 mmol) and acetic acid (0.040 mL, 0.75 mmol). After letting the mixture react for about 2 min, $NaBH(OAc)_3$ (0.159 g, 0.750 mmol) was added. The resulting mixture was shaken for 48 h. After removal of the solution, the resin was washed with three portions (20 mL) each of THF, CH_3OH, THF, and CH_2Cl_2. The product was cleaved from support and purified following Procedure D to afford 13.4 mg (30%) of the TFA salt **1.38** as a white powder. ^1H NMR (500 MHz, DMSO-d_6): δ 0.71 (d, 3H, J = 7.0), 0.84 (t, 3H, J = 7.2), 1.03 (d, 3H, J = 7.0), 1.12-1.38 (m, 4H), 1.67 (s, 3H), 2.19-2.31 (m, 2H), 2.37 (s, 3H), 2.67 (sept, 1H, J = 7.0), 3.58 (s, 2H), 3.74 (s, 3H), 4.01-4.08 (m, 2H), 5.60 (dd, 1H, J = 6.0, 9.5), 6.93 (d, 2H, J = 8.5), 7.25 (d, 2H, J = 8.5), 7.49 (dd, 1H, J = 2.0, 8.5), 7.78 (d, 1H, J = 2.0), 7.82 (d, 1H, J = 8.5), 8.59 (s, 1H), 8.93-9.12 (m, 2H), 11.11 (s, 1H), 12.51 (br s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{33}H_{42}N_5O_6$, 604.3135; found, 604.3124.



Amine substrate 1.39. Procedure A was followed using resin **1.15** (0.421 g, 0.150 mmol), propargylamine **1.46** (0.057 g, 0.23 mmol), *i*-Pr_2EtN (2.6 mL, 15 mmol), and CuI (0.086 g, 0.45 mmol) in THF (8.2 mL) to afford 51.0 mg (54%) of the TFA salt **1.39** as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.75 (d, 3H, *J* = 6.6), 0.84 (t, 3H, *J* = 7.2), 1.07 (d, 3H, *J* = 6.6), 1.12-1.39 (m, 4H), 1.73 (s, 3H), 2.21-2.34 (m, 2H), 2.37 (s, 3H), 2.70 (sept, 1H, *J* = 6.6), 3.59 (s, 2H), 3.98-4.06 (m, 1H), 4.31-4.39 (m, 1H), 5.62 (dd, 1H, *J* = 6.0, 9.4), 7.49 (dd, 1H, *J* = 2.0, 8.8), 7.61 (dd, 1H, *J* = 4.4, 8.4), 7.75 (dd, 1H, *J* = 1.6, 8.8), 7.80-7.85 (m, 2H), 7.96 (d, 1H, *J* = 1.5), 8.06 (d, 1H, *J* = 8.8), 8.40 (d, 1H, *J* = 7.6), 8.65 (s, 1H), 8.96 (dd, 1H, *J* = 1.6, 4.0), 9.22-9.36 (m, 2H), 11.13 (s, 1H), 12.65 (br s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{35}H_{41}N_6O_5$, 625.3138; found, 625.3146.



Amine substrate 1.40. Procedure A was followed using resin **1.15** (0.421 g, 0.150 mmol), propargylamine **1.73b** (0.058 g, 0.23 mmol), *i*-Pr_2EtN (2.6 mL, 15 mmol), and CuI (0.086 g, 0.45 mmol) in THF (8.2 mL) to afford 34.0 mg (36%) of the TFA salt **1.40** as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.74 (d, 3H, *J* = 6.5), 0.84 (t, 3H, *J* = 7.0), 1.06 (d, 3H, *J* = 6.5), 1.12-1.39 (m, 4H), 1.72 (s, 3H), 2.21-2.34 (m, 2H), 2.36 (s, 3H), 2.70 (sept, 1H, *J* = 6.5), 3.58 (s, 2H), 3.94-4.02 (m, 1H), 4.26-4.33 (m, 1H), 5.64 (dd, 1H, *J* = 6.0, 9.5), 7.53 (dd, 2H, *J* = 1.5, 8.5), 7.78 (d, 1H, *J* = 1.5), 7.81 (d, 1H, *J* = 8.5), 8.08-8.14 (m, 2H), 8.63 (s, 1H), 9.31 (br s, 2H), 9.45 (s, 1H), 11.21 (s, 1H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{33}H_{39}N_6O_5S$, 631.2703; found, 631.2691.

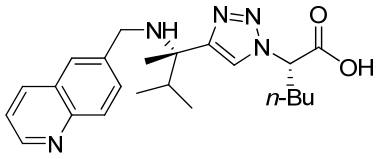
General Procedures for the Synthesis of Inhibitors

General synthesis of 1,2,3-triazole compounds (Procedure E). This procedure was adapted from Sharpless.[37] To a 0.25 M suspension of alkyne (1 equiv) and azide (1 equiv) in a 1:1 mixture of water and *tert*-butyl alcohol was added sodium ascorbate (1 equiv of a freshly prepared 1.0 M solution in water) followed by copper(II) sulfate pentahydrate (0.1 equiv of a freshly prepared 0.3 M solution in water). The heterogeneous mixture was stirred vigorously overnight. Water was added and extracted with EtOAc (3x). The organic layers were combined, washed with saturated NaCl (1x), dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to 95:5 over 55 min; 10 mL/min;

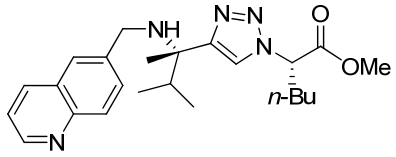
254 nm detection for 65 min] and lyopholized to afford the TFA salt of the product. The free amine of the product was obtained by dissolving the TFA salt of the product in saturated aqueous $NaHCO_3$ and extracting with CH_2Cl_2 (4x). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

General synthesis of acyl- and aryl-oxymethyl ketone azides 1.54a-c (Procedure F). To a 0.2 M solution of benzoic acid or phenol (3.1 - 4.0 equiv) in DMF at 0 ºC was added potassium fluoride (3.0 - 4.0 equiv), and the reaction mixture was stirred for 10 min. Bromomethyl ketone **1.55** (1.0 equiv) was then added in a small amount of DMF. The reaction mixture was stirred at 0 ºC for 0.5-3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water (1x), saturated $NaHCO_3$ (1x), water (2x), and brine (1x). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography afforded the pure product.

Synthesis of Vinyl Sulfone Inhibitor 1.45 (Scheme 1.3)

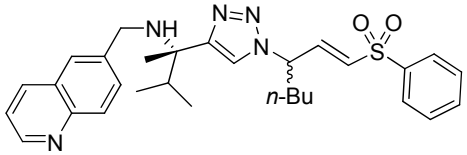


Carboxylic acid 1.48. Procedure E was followed using propargyl amine **1.46** (0.063 g, 0.25 mmol), azide **1.47** (0.040 g, 0.25 mmol), sodium ascorbate (0.25 mL, 0.25 mmol), copper(II) sulfate pentahydrate (0.084 mL, 0.025 mmol) in 1:1 *t*BuOH:H_2O (1.0 mL) to afford 0.151 g (89%) of the TFA salt **1.48** as a sticky yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.74 (d, 3H, *J* = 6.9), 0.81 (t, 3H, *J* = 7.5), 0.97-1.39 (m, 4H), 1.06 (d, 3H, *J* = 6.9), 1.70 (s, 3H), 2.13-2.29 (m, 2H), 2.07 (sept, 1H, *J* = 6.9), 3.92-4.07 (m, 1H), 4.28-4.41 (m, 1H), 5.49 (dd, 1H, *J* = 6.3, 9.6), 7.64 (dd, 1H, *J* = 4.1, 8.4), 7.74 (dd, 1H, *J* = 1.8, 8.7), 7.97 (d, 1H, *J* = 1.5), 8.07 (d, 1H, *J* = 8.7), 8.46 (d, 1H, *J* = 8.4), 8.54 (s, 1H), 8.99 (d, 1H, *J* = 4.1), 9.24-9.49 (br s, 2H). ^{13}C-NMR (125 MHz, DMSO-d_6): δ 13.7, 15.7, 16.3, 17.8, 21.3, 27.5, 30.6, 33.6, 45.8, 62.5, 63.7, 122.1, 125.0, 127.4, 128.4, 130.3, 130.5, 131.8, 137.1, 145.4, 146.5, 150.9, 170.3. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{23}H_{32}N_5O_2$, 410.2556; found, 410.2566.



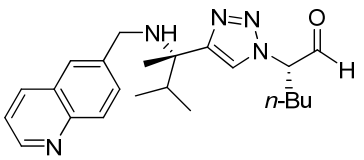
Methyl ester 1.49. A 0.2 M stirred solution of carboxylic acid **1.48** (0.050 g, 0.095 mmol) in THF (0.5 mL) was cooled to 0 ºC. Excess diazomethane was introduced *in situ* from Diazald (0.164 g, 0.764 mmol), according to literature procedure.[34] After addition of the diazomethane, the solution was stirred at 0 ºC for 15 min. The solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography (1-5% MeOH/CH_2Cl_2) to afford 30.0 mg (75%) of **1.49** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (d, 3H, *J* = 7.0), 0.88 (t, 3H, *J* = 7.0), 1.02 (d, 3H, *J* = 7.0), 1.11-1.44 (m, 4H), 1.50 (s, 3H), 1.89 (br s, 1H), 2.05-2.29 (m, 3H), 3.61 (d, 1H, *J* = 12.5), 3.74-3.80 (m, 4H), 5.38 (dd, 1H, *J* =

5.5, 10.0), 7.37 (dd, 1H, *J* = 4.0, 8.5), 7.62 (s, 1H), 7.68 (dd, 1H, *J* = 1.5, 8.5), 7.74 (s, 1H), 8.02 (d, 1H, *J* = 8.5), 8.11 (d, 1H, *J* = 8.5), 8.86 (d, 1H, *J* = 4.0). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.0, 17.4, 18.1, 19.6, 22.1, 28.0, 32.7, 37.4, 47.5, 53.1, 58.6, 62.8, 121.0, 121.3, 126.2, 128.4, 129.5, 130.8, 136.0, 140.0, 147.8, 150.1, 153.5, 170.0. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{24}H_{34}N_5O_2$, 424.2712; found, 424.2724.

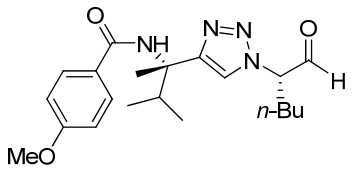


Vinyl sulfone 1.45. A 0.2 M solution of methyl ester **1.49** (28 mg, 0.067 mmol) in diethyl ether (0.3 mL) and a 0.6 M solution of DIBAL (0.048 mL, 0.27 mmol) in diethyl ether (0.4 mL) were cooled in a -78 ºC acetone-dry ice bath. The DIBAL solution was cannula transferred to the methyl ester solution, and the resulting solution was stirred for 1 h at -78 ºC. The reaction was quenched at -78 ºC by adding methanol (0.4 mL) and then acetic acid (0.060 mL, 1.0 mmol). After the reaction mixture was stirred for 5 min, a saturated sodium tartrate solution (0.8 mL) was added. After stirring for 20 min, the reaction mixture was diluted with EtOAc (5 mL) and water (2 mL). The aqueous layer was extracted EtOAc (3 x 5 mL). The organic washes were combined and extracted once with water (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The aldehyde was taken on to the next step without purification.

To a round-bottom flask containing LiBr (4.8 mg, 0.055 mmol) and diethyl (phenylsulfonyl)methyl]phosphonate[38] (13 mg, 0.046 mmol) was added acetonitrile (1.2 mL) and triethylamine (0.006 mL, 0.05 mmol). After cooling the reaction mixture to -40 ºC in an acetonitrile-dry ice bath, the aldehyde (0.018 g, 0.050 mmol) in acetonitrile (0.6 mL) was added dropwise. The reaction mixture was stirred for 36 h at -40 ºC, and then the reaction was quenched by adding 1M HCl (0.4 mL) and water (0.8 mL) at 0 ºC. The aqueous layer was then basified to pH=10 with 1M NaOH and extracted with EtOAc (5 x 2 mL). The organic layers were combined and washed with saturated NaCl (1 x 2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to 95:5 over 55 min; 10 mL/min; 254 nm detection for 65 min] and lyophilized to afford 4.6 mg (11%; 2 steps) of a 1:1 mixture of diastereomers of the TFA salt **1.45** as a sticky clear solid. The inhibitor was > 99% pure as determined by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in two solvent systems: CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min; CH_3OH/H_2O, 5:95 to 95:5 over 20 min, 95:5 for 10 min). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.70 (d, 3H, *J* = 6.5), 0.76 (t, 1.5H, *J* = 7.2), 0.77 (t, 1.5H, *J* = 7.2), 0.88-1.31 (m, 4H), 1.04 (d, 3H, *J* = 6.5), 1.68 (s, 3H), 1.99-2.12 (m, 2H), 2.64-2.79 (m, 1H), 4.01-4.09 (m, 1H), 4.28-4.38 (m, 1H), 5.51-5.60 (m, 1H), 6.94 (dd, 0.5H, *J* = 1.1, 15.1), 6.96 (dd, 0.5H, *J* = 1.1, 15.1), 7.17 (dd, 0.5H, *J* = 1.5, 15.1), 7.18 (dd, 0.5H, *J* = 1.5, 15.1), 7.58-7.66 (m, 3H), 7.70-7.75 (m, 2H), 7.83-7.87 (m, 2H), 7.96-7.99 (m, 1H), 8.05 (d, 0.5H, *J* = 8.7), 8.06 (d, 0.5H, *J* = 8.7), 8.39-8.43 (m, 1H), 8.55 (s, 0.5H), 8.57 (s, 0.5H), 8.96 (dd, 1H, *J* = 2.0, 4.3), 9.23-9.40 (m, 2H). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{30}H_{38}N_5O_2S$, 532.2746; found, 532.2745.

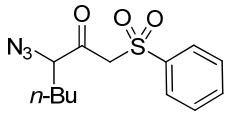


Aldehyde 1.44. Starting material was recovered from the Horner-Wadworth-Emmons homologation above by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to 95:5 over 55 min; 10 mL/min; 254 nm detection for 65 min] and lyophilization to afford 4.9 mg (19%) of aldehyde **1.44**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75-0.94 (m, 6H), 1.03 (d, 3H, *J* = 6.8), 1.13-1.44 (m, 4H), 1.58 (s, 3H), 1.71-1.80 (m, 2H), 2.22-2.36 (m, 1H), 3.68 (d, 1H, *J* = 12.4), 3.89 (d, 1H, *J* = 12.8), 5.21 (dd, 1H, *J* = 4.8, 9.6), 7.42 (dd, 1H, *J* = 4.4, 8.4), 7.61-7.82 (m, 3H), 8.07 (d, 1H, *J* = 8.4), 8.17 (d, 1H, *J* = 7.6), 8.90 (d, 1H, 4.0), 9.75 (s, 1H). MS (ESI): *m/z* 412 $[(M+H_2O)H]^+$.



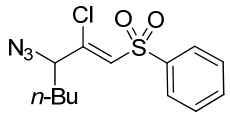
Aldehyde 1.43. This aldehyde was prepared in 4 steps from propargyl amine **1.16** and 4-methoxybenzoic acid anhydride according to the procedure previously reported for the synthesis of 1,2,3-triazole aldehyde inhibitors.[10] ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (d, 3H, *J* = 6.5), 0.87 (t, 3H, *J* = 7.0), 0.97 (d, 3H, *J* = 6.5), 0.99-1.40 (m, 4H), 1.85 (s, 3H), 2.00-2.09 (m, 1H), 2.21-2.29 (m, 1H), 2.93 (sextet, 1H, *J* = 7.0), 3.83 (s, 3H), 5.13 (dd, 1H, *J* = 5.0, 10), 6.90 (d, 2H, *J* = 6.5), 7.61 (s, 1H), 7.71-7.79 (m, 3H), 9.72 (s, 1H). MS (ESI): *m/z* 405 $[(M+H_2O)H]^+$.

Synthesis of β-chloro Vinyl Sulfone Inhibitor 1.50 (Scheme 1.4)



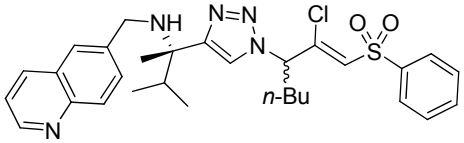
β-Keto sulfone 1.52. This procedure was adapted from Chun.[39] To a 0.6 M solution of methyl phenyl sulfone (1.30 g, 8.31 mmol) in THF (14 mL) at 0 ºC was added dropwise *n*-butyllithium (7.55 mL, 16.6 mmol). The reaction mixture was stirred at 0 ºC for 30 min and then cooled to -78 ºC. A 0.6 M solution of methyl ester **1.51** (0.711 g, 4.15 mmol) in THF (6.9 mL) was added dropwise. The reaction mixture was stirred at -78 ºC for 3 h. Saturated aqueous NH_4Cl (10 mL) was added and the product was extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (5-25% EtOAc/hexanes) to afford 0.300 g (25%) of **1.52** as a pale yellow solid. mp 64-66 ºC. IR ν_{max} (cm^{-1}): 2959, 2935, 2873, 2104, 1728, 1321, 1155. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, *J* = 7.2), 1.28-1.46 (m, 4H), 1.52-1.90 (m, 2H), 4.13 (dd, 1H, *J* = 4.8, 8.4), 4.26 (d, 1H, *J* = 13.8), 4.42 (d, 1H, *J* = 13.8), 7.56-7.64 (m, 2H), 7.68-7.75 (m, 1H), 7.88-7.93

(m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.0, 22.4, 27.9, 29.9, 63.7, 68.6, 128.6, 129.6, 134.7, 138.7, 195.5. HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{13}H_{17}N_3O_3SLi$, 302.1151; found, 302.1142.



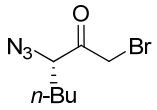
β-Chloro sulfone 1.53. The preparation of the vinyl triflate was adapted from Mastalerz.[40] To a 0.1 M solution of β-keto sulfone **1.52** (0.137 g, 0.460 mmol) in CH_2Cl_2 (4.6 mL) at -20 ºC were added triflic anhydride (0.086 mL, 0.51 mmol) and *i*-Pr_2EtN (0.089 mL, 0.51 mmol). The reaction mixture was stirred for 1 h while warming to room temperature and then diluted with CH_2Cl_2 (10 mL). The organic layer was washed with water (1 x 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The *i*-Pr_2EtN triflate salt was triturated away with ether. The product was taken on to the next step without further purification.

To a 0.2 M solution of the vinyl triflate (0.098 g, 0.23 mmol) in THF (1.2 mL) at 0 ºC was added tetrabutylammonium chloride (0.192 g, 0.690 mmol). The reaction mixture was warmed to room temperature and stirred for 19 h. Saturated aqueous NH_4Cl (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with saturated NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (5-15% EtOAc/hexanes) afforded 0.037 g (51%) of **1.53** as a pale yellow oil. IR ν_{max} (cm^{-1}): 3041, 2958, 2863, 2100, 1604, 1324, 1149. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 6.8), 1.14-1.36 (m, 4H), 1.62-1.82 (m, 2H), 3.95-4.02 (m, 1H), 6.90 (s, 1H), 7.53-7.59 (m, 2H), 7.64-7.69 (m, 1H), 7.96-8.01 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.0, 22.2, 27.4, 31.9, 67.1, 128.2, 129.4, 130.0, 134.2, 140.5, 147.1. HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{13}H_{16}N_3O_2SClLi$, 320.0812; found, 320.0815.

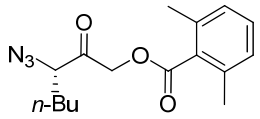


β-Chloro vinyl sulfone 1.50. Procedure E was followed using propargyl amine **1.46** (0.025 g, 0.10 mmol), azide **1.53** (0.031 g, 0.10 mmol), sodium ascorbate (0.10 mL, 0.10 mmol), copper(II) sulfate pentahydrate (0.033 mL, 0.010 mmol) in 1:1 *t*BuOH:H_2O (0.4 mL) to afford 26.6 mg (51%) of a 0.7:0.3 mixture of diastereomers of **1.50** as a clear oil. Olefin geometry was confirmed by NOE spectroscopy (vide infra). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (d, 2.1H, *J* = 6.8), 0.75 (d, 0.9H, *J* = 6.8), 0.86 (t, 3H, *J* = 7.2), 0.98 (d, 3H, *J* = 6.8), 1.08-1.39 (m, 4H), 1.46 (s, 3H), 1.76 (br s, 1H), 2.09-2.13 (m, 3H), 3.53 (d, 1H, *J* = 12.8), 3.73 (d, 1H, *J* = 12.8), 5.18-5.25 (m, 1H), 6.80 (s, 0.3H), 6.81 (s, 0.7H), 7.38 (dd, 1H, *J* = 4.4, 8.4), 7.42 (s, 1H), 7.51 (t, 2H, *J* = 7.6), 7.58-7.68 (m, 2H), 7.71 (s, 1H), 7.90-7.95 (m, 2H), 8.03 (d, 1H, *J* = 8.4), 8.12 (d, 1H, *J* = 8.0), 8.87 (dd, 1H, *J* = 1.6, 4.4). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{30}H_{37}N_5O_2SCl$, 566.2357; found, 566.2357. Anal. Calcd for $C_{30}H_{36}N_5O_2SCl$: C, 63.64; H, 6.41; N, 12.37. Found: C, 63.30; H, 6.56; N, 11.99.

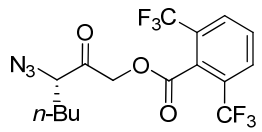
Synthesis of Aryl- and Acyl-oxymethyl Ketone Inhibitors 1.56-1.62 (Scheme 1.5)



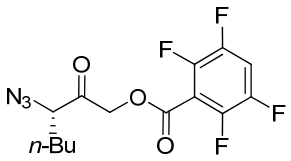
Bromomethyl ketone azide 1.55. This procedure was adapted from a prior publication.[41] Isobutylchloroformate (0.690 mL, 5.25 mmol) was added to a 0.1 M solution of azido acid **1.47** (0.750 g, 4.77 mmol) and *N*-methyl morpholine (0.580 mL, 5.25 mmol) in THF (48 mL) at -40 ºC. The reaction mixture was stirred for 20 min and then cannula filtered into a flask at 0 ºC to remove the white solid. Excess diazomethane, prepared from Diazald (3.17 g, 14.8 mmol), was introduced *in situ*, according to the literature procedure,[34] while the flask was maintained at 0 ºC. After addition of the diazomethane, the reaction flask was stoppered and was maintained at 0 ºC in a refrigerator overnight. The reaction mixture was treated with 48% aqueous HBr (0.981 mL) and stirred for 15 min at 0 ºC. After addition of the HBr, N_2 gas evolution was observed. The reaction mixture was diluted with EtOAc (50 mL) and was then washed with 10 wt% citric acid (2 x 10 mL), saturated $NaHCO_3$ (2 x 20 mL), and saturated NaCl (1 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (1-5% EtOAc/hexanes) afforded 0.908 g (81%) of **1.55** as a faintly yellow oil. The purified product was contaminated with 10% of the methyl ester as determined by ^{1}H NMR. The methyl ester, however, was unreactive under the subsequent reaction conditions and was therefore easily removed later in the synthetic sequence. Only the peaks for the desired product are reported in the NMR spectra. IR ν_{max} (cm^{-1}): 2960, 2874, 2106, 1821, 1739. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 6.5), 1.30-1.51 (m, 4H), 1.68-1.92 (m, 2H), 3.99-4.18 (m, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.0, 22.4, 28.0, 30.9, 32.0, 66.2, 199.0. MS (ESI): *m/z* 205, 207 $[(M-N_2)H]^+$.



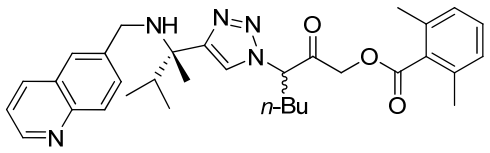
Acyloxymethyl ketone azide 1.54a. Procedure F was followed using bromomethyl ketone **1.55** (0.10 g, 0.43 mmol), 2,6-dimethylbenzoic acid (0.257, 1.71 mmol), and potassium fluoride (0.0990 g, 1.71 mmol). The reaction mixture was stirred for 30 min. The crude reaction mixture was purified by column chromatography (1-5% EtOAc/hexanes) to afford 0.082 g (63%) of **1.54a** as a clear oil. IR ν_{max} (cm^{-1}): 2960, 2932, 2873, 2106, 1743, 1596. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, 3H, J = 7.0), 1.32-1.52 (m, 4H), 1.79-1.97 (m, 2H), 2.41 (s, 6H), 4.02 (dd, 1H, J = 5.0, 8.0), 5.04 (d, 1H, J = 17.5), 5.11 (d, 1H, J = 17.0), 7.05 (d, 2H, J = 7.5), 7.21 (t, 1H, J = 7.5). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.0, 20.1, 22.4, 27.8, 30.9, 66.7, 66.8, 127.9, 130.0, 132.5, 135.9, 169.15, 200.4. HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{16}H_{21}N_3O_3Li$, 310.1743; found, 310.1749.



Acyloxymethyl ketone azide 1.54b. Procedure F was followed using bromomethyl ketone **1.55** (0.250 g, 1.07 mmol), 2,6-bis(trifluoromethyl)-benzoic acid (0.854, 3.31 mmol), and potassium fluoride (0.186 g, 3.20 mmol). The reaction mixture was stirred for 30 min. The crude reaction mixture was purified by column chromatography (1-10% EtOAc/hexanes) to afford 0.321 g (73%) of **1.54b** as a clear oil. IR ν_{max} (cm^{-1}): 2962, 2935, 2876, 2107, 1744, 1594. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.0), 1.29-1.51 (m, 4H), 1.75-1.96 (m, 2H), 4.04 (dd, 1H, *J* = 4.8, 8.4), 5.06 (d, 1H, *J* = 17.6), 5.13 (d, 1H, *J* = 17.6), 7.76 (t, 1H, *J* = 8.0), 7.96 (d, 2H, *J* = 8.0). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 27.8, 30.6, 66.4, 68.2, 122.9 (q, *J* = 273), 129.4, 129.7, 130.2 (q, *J* = 4.0), 131.0, 164.4, 199.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.7 (s, 6F). HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{16}H_{15}N_3O_3F_6Li$, 418.1178; found, 418.1178.

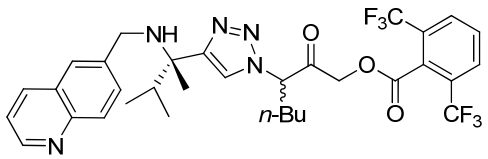


Aryloxymethyl ketone azide 1.54c. Procedure F was followed using bromomethyl ketone **1.55** (0.10 g, 0.43 mmol), 2,3,5,6-tetrafluorophenol (0.220, 1.32 mmol), and potassium fluoride (0.0740 g, 1.28 mmol). The reaction mixture was stirred for 3 h. The crude reaction mixture was purified by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to 95:5 over 55 min; 10 mL/min; 254 nm detection for 65 min] and lyopholized to afford 0.062 g (45%) of **1.54c** as a clear oil. IR ν_{max} (cm^{-1}): 2962, 2935, 2876, 2106, 1743, 1642, 1518. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, 3H, *J* = 7.0), 1.32-1.51 (m, 4H), 1.74-1.83 (m, 1H), 1.89-1.97 (m, 1H), 4.14 (dd, 1H, *J* = 4.5, 8.5), 5.00 (d, 1H, *J* = 17.5), 5.05 (d, 1H, *J* = 17.5), 6.78-6.85 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 28.0, 30.5, 65.8, 75.6 (t, *J* = 3.0), 100.2 (t, *J* = 18.0), 137.0-137.2 (m), 140.6 (dm, *J* = 247), 146.5 (dm, *J* = 247), 201.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.3 - -156.2 (m, 2F), -138.9 - -138.4 (m, 2F). HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{13}H_{13}N_3O_2F_4Li$, 326.1104; found, 326.1106.

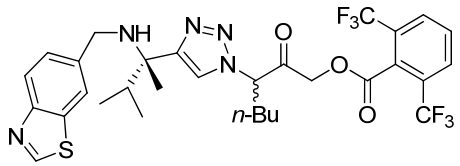


Acyloxymethyl ketone inhibitor 1.56. Procedure E was followed using propargyl amine **1.46** (0.025 g, 0.10 mmol), azide **1.54a** (0.031 g, 0.10 mmol), sodium ascorbate (0.10 mL, 0.10 mmol), copper(II) sulfate pentahydrate (0.033 mL, 0.010 mmol) in 1:1 *t*BuOH:H_2O (0.4 mL) to afford 19.3 mg (35%) of a 1:1 mixture of diastereomers of **1.56** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, 3H, *J* = 7.0), 0.86 (t, 1.5H, *J* = 7.0), 0.88 (t, 1.5H, *J* = 7.0), 1.02 (d, 1.5H, *J* = 6.5), 1.03 (d, 1.5H, *J* = 6.5), 1.11-1.43 (m, 4H), 1.50 (s, 1.5H), 1.52 (s, 1.5H), 1.85 (br s, 1H), 2.08-2.24 (m, 2H), 2.27-2.36 (m, 1H), 2.35 (s, 3H), 2.36 (s, 3H), 3.61 (d, 0.5H, *J* = 13.0),

3.62 (d, 0.5H, J = 13.0), 3.78 (d, 1H, J = 13.0), 4.84 (d, 0.5H, J = 17.0), 4.85 (d, 0.5H, J = 17.0), 4.95 (d, 1H, J = 17.0), 5.44 (dd, 1H, J = 5.0, 10.0), 7.03 (d, 2H, J = 7.5), 7.21 (t, 1H, J = 7.5), 7.349 (dd, 0.5H, J = 4.5, 8.5), 7.353 (dd, 0.5H, J = 4.5, 8.5), 7.60 (d, 1H, J = 5.5), 7.676 (dd, 0.5H, J = 2.0, 9.0), 7.684 (dd, 0.5H, J = 2.0, 9.0), 7.73 (s, 1H), 8.02 (dd, 1H, J = 2.0, 9.0), 8.08 (d, 1H, J = 8.0), 8.86 (d, 1H, J = 4.5). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{33}H_{42}N_5O_3$, 556.3288; found, 556.3279. Anal. Calcd for $C_{33}H_{41}N_5O_3$: C, 71.32; H, 7.44; N, 12.60. Found: C, 70.91; H, 7.62; N, 12.56.

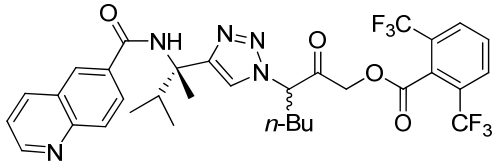


Acyloxymethyl ketone inhibitor 1.57. Procedure E was followed using propargyl amine **1.46** (0.019 g, 0.075 mmol), azide **1.54b** (0.031 g, 0.075 mmol), sodium ascorbate (0.075 mL, 0.075 mmol), copper(II) sulfate pentahydrate (0.025 mL, 0.0075 mmol) in 1:1 *t*BuOH:H_2O (0.3 mL) to afford 24.6 mg (49%) of a 1:1 mixture of diastereomers of **1.57** as a white sticky solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.69-0.81 (m, 6H), 0.95 (d, 3H, J = 6.8), 1.11-1.33 (m, 4H), 1.39 (s, 3H), 2.05-2.34 (m, 4H), 3.51 (d, 1H, J = 13.2), 3.68 (d, 1H, J = 13.2), 5.13 (d, 0.5H, J = 17.2), 5.14 (d, 0.5H, J = 17.2), 5.27 (d, 0.5H, J = 17.2), 5.28 (d, 0.5H, J = 17.2), 5.71 (dd, 1H, J = 4.4, 10.8), 7.46 (dd, 0.5H, J = 4.0, 8.4), 7.47 (dd, 0.5H, J = 4.0, 8.4), 7.67 (d, 1H, J = 8.8), 7.80 (s, 1H), 7.91 (d, 1H, J = 8.8), 7.99 (t, 1H, J = 8.0), 8.17 (s, 1H), 8.21-8.30 (m, 3H), 8.80-8.85 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.7 (s, 6F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{33}H_{36}N_5O_3F_6$, 664.2722; found, 664.2710. Anal. Calcd for $C_{33}H_{35}N_5O_3F_6$: C, 59.72; H, 5.32; N, 10.55. Found: C, 59.58; H, 5.34; N, 10.51.

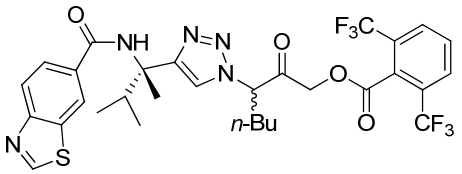


Acyloxymethyl ketone inhibitor 1.58. Procedure E was followed using propargyl amine **1.73b** (0.021 g, 0.082 mmol), azide **1.54b** (0.034 g, 0.082 mmol), sodium ascorbate (0.082 mL, 0.082 mmol), copper(II) sulfate pentahydrate (0.027 mL, 0.0082 mmol) in 1:1 *t*BuOH:H_2O (0.33 mL) to afford 24.4 mg (44%) of a 1:1 mixture of diastereomers of **1.58** as a white sticky solid. The inhibitor was > 99% pure as determined by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in two solvent systems: CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min; CH_3OH/H_2O, 5:95 to 95:5 over 20 min, 95:5 for 10 min). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (d, 3H, J = 7.0), 0.83 (t, 1.5H, J = 7.0), 0.85 (t, 1.5H, J = 7.0), 1.006 (d, 1.5H, J = 7.0), 1.010 (d, 1.5H, J = 7.0), 1.07-1.41 (m, 4H), 1.48 (s, 1.5H), 1.49 (s, 1.5H), 1.72 (br s, 1H), 2.02-2.32 (m, 3H), 3.55 (d, 0.5H, J = 12.5), 3.56 (d, 0.5H, J = 12.5), 3.73 (d, 1H, J = 12.5), 4.90-5.01 (m, 2H), 5.495 (dd, 0.5H, J = 5.0, 10.0), 5.500 (dd, 0.5H, J = 5.0, 10.0), 7.45 (dd, 0.5H, J = 1.5, 8.5), 7.46 (dd, 0.5H, J = 1.5, 8.5), 7.57 (s, 0.5H), 7.58 (s, 0.5H), 7.76 (t, 1H, J = 8.5), 7.92-7.98 (m, 3H), 8.02 (d, 0.5H, J = 8.5), 8.03 (d, 0.5H, J = 8.5),

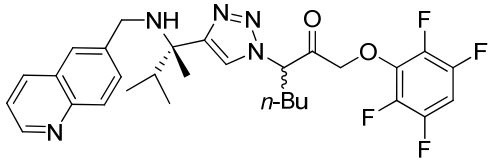
8.931 (s, 0.5H), 8.933 (s, 0.5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.7 (s, 6F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{31}H_{34}N_5O_3F_6S$, 670.2287; found, 670.2288.



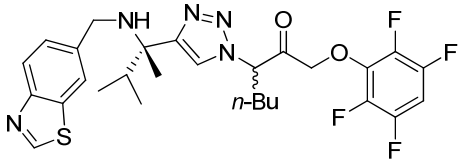
Acyloxymethyl ketone inhibitor 1.59. Procedure E was followed using propargyl amide **1.67** (0.040 g, 0.15 mmol), azide **1.54b** (0.062 g, 0.15 mmol), sodium ascorbate (0.15 mL, 0.15 mmol), copper(II) sulfate pentahydrate (0.050 mL, 0.015 mmol) in 1:1 *t*BuOH:H_2O (0.6 mL) to afford 22.7 mg (22%) of a 0.6:0.4 mixture of diastereomers of **1.59** as a white sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80-0.89 (m, 6H), 0.95 (d, 1.8H, *J* = 6.8), 0.99 (d, 1.2H, *J* = 6.8), 1.10-1.43 (m, 4H), 1.97 (s, 1.2H), 1.98 (s, 1.8H), 2.06-2.16 (m, 1H), 2.24-2.35 (m, 1H), 2.96-3.08 (m, 1H), 4.96 (s, 2H), 5.51 (dd, 1H, *J* = 5.0, 10.0), 7.47 (dd, 1H, *J* = 4.0, 8.4), 7.63 (s, 0.6H), 7.70 (s, 0.4H), 7.71 (s, 1H), 7.77 (t, 1H, *J* = 8.0), 7.95 (d, 2H, *J* = 8.0), 8.09-8.13 (m, 1H), 8.14 (s, 0.6H), 8.17 (s, 0.4H), 8.24-8.28 (m, 1H), 8.31 (d, 0.6H, *J* = 2.0), 8.32 (d, 0.4H, *J* = 2.0), 8.98 (dd, 1H, *J* = 1.6, 4.4) . ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.67 (s, 3.6F), -58.68 (s, 2.4F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{33}H_{34}N_5O_4F_6$, 678.2515; found, 678.2521. Anal. Calcd for $C_{33}H_{33}N_5O_4F_6$: C, 58.49; H, 4.91; N, 10.33. Found: C, 58.39; H, 5.07; N, 10.24.



Acyloxymethyl ketone inhibitor 1.60. Procedure E was followed using propargyl amide **1.68** (0.041 g, 0.15 mmol), azide **1.54b** (0.062 g, 0.15 mmol), sodium ascorbate (0.15 mL, 0.15 mmol), copper(II) sulfate pentahydrate (0.050 mL, 0.015 mmol) in 1:1 *t*BuOH:H_2O (0.6 mL) to afford 22.2 mg (22%) of a 1:1 mixture of diastereomers of **1.60** as a white sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79-0.88 (m, 6H), 0.94 (d, 1.5H, *J* = 6.8), 0.98 (d, 1.5H, *J* = 6.8), 1.10-1.47 (m, 4H), 1.96 (s, 3H), 2.05-2.33 (m, 2H), 2.93-3.05 (m, 1H), 4.96 (m, 2H), 5.51 (dd, 1H, *J* = 4.8, 10.0), 7.58 (s, 0.5H), 7.61 (s, 0.5H), 7.70 (s, 1H), 7.77 (t, 1H, *J* = 8.0), 7.92-7.99 (m, 3H), 8.16 (s, 0.5H), 8.18 (s, 0.5H), 8.47 (m, 1H), 9.11 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.68 (s, 3.6F), -58.67 (s, 2.4F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{31}H_{32}N_5O_4SF_6$, 684.2079; found, 684.2083. Anal. Calcd for $C_{31}H_{31}N_5O_4SF_6$: C, 54.46; H, 4.57; N, 10.24; S, 4.69. Found: C, 54.22; H, 4.43; N, 10.00; S, 4.80.

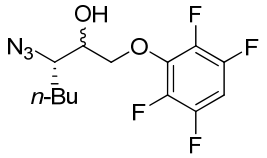


Aryloxymethyl ketone inhibitor 1.61. Procedure E was followed using propargyl amine **1.46** (0.020 g, 0.075 mmol), azide **1.54c** (0.024 g, 0.075 mmol), sodium ascorbate (0.075 mL, 0.075 mmol), copper(II) sulfate pentahydrate (0.025 mL, 0.0075 mmol) in 1:1 *t*BuOH:H_2O (0.3 mL) to afford 21.0 mg (49%) of a 1:1 mixture of diastereomers of **1.61** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, 3H, *J* = 6.8), 0.85 (t, 1.5H, *J* = 7.0), 0.87 (t, 1.5H, *J* = 7.0), 1.02 (d, 3H, *J* = 6.8), 1.07-1.45 (m, 4H), 1.50 (s, 1.5H), 1.51 (s, 1.5H), 1.79 (br s, 1H), 1.98-2.13 (m, 1H), 2.19 (sept, 1H, *J* = 6.8), 2.22-2.46 (m, 1H), 3.59 (d, 1H, *J* = 12.8), 3.77 (d, 0.5H, *J* = 12.8), 3.78 (d, 0.5H, *J* = 12.8), 4.93 (s, 2H), 5.66 (dd, 0.5H, *J* = 4.8, 10.4), 5.67 (dd, 0.5H, *J* = 4.8, 10.4), 6.76-6.84 (m, 1H), 7.37 (dd, 1H, *J* = 4.4, 8.4), 7.57 (s, 0.5H), 7.58 (s, 0.5H), 7.65-7.70 (m, 1H), 7.73 (s, 1H), 8.01 (d, 0.5H, *J* = 8.4), 8.03 (d, 0.5H, *J* = 8.4), 8.09-8.13 (m, 1H), 8.84-8.88 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 - -156.1 (m, 2F), -138.0 - -137.9 (m, 2F). HRMS-FAB (m/z): $[MNa]^+$ calcd for $C_{30}H_{33}N_5O_2F_4Na$, 594.2468; found, 594.2453. Anal. Calcd for $C_{30}H_{33}N_5O_2F_4$: C, 63.04; H, 5.82; N, 12.25. Found: C, 62.74; H, 5.95; N, 11.92.

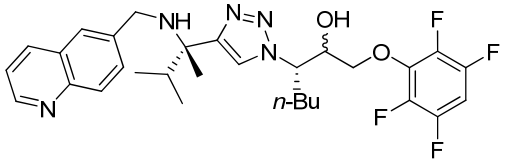


Aryloxymethyl ketone inhibitor 1.62. Procedure E was followed using propargyl amine **1.73b** (0.039 g, 0.15 mmol), azide **1.54c** (0.048 g, 0.15 mmol), sodium ascorbate (0.15 mL, 0.15 mmol), copper(II) sulfate pentahydrate (0.050 mL, 0.015 mmol) in 1:1 *t*BuOH:H_2O (0.6 mL) to afford 31.5 mg (36%) of a 0.6:0.4 mixture of diastereomers of **1.62** as a clear sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, 3H, *J* = 6.8), 0.87 (t, 3H, *J* = 7.2), 1.00 (d, 3H, *J* = 6.8), 1.07-1.45 (m, 4H), 1.480 (s, 1.8H), 1.485 (s, 1.2H), 1.90 (br s, 1H), 1.98-2.35 (m, 3H), 3.55 (d, 1H, *J* = 12.4), 3.73 (d, 1H, *J* = 12.4), 4.92 (s, 2H), 5.66 (dd, 1H, *J* = 4.8, 10.4), 6.76-6.84 (m, 1H), 7.44 (dd, 1H, *J* = 2.0, 8.4), 7.56 (s, 0.4H), 7.57 (s, 0.6H), 7.93 (s, 1H), 8.02 (d, 0.4H, *J* = 8.4), 8.03 (d, 0.6H, *J* = 8.4), 8.93 (s, 0.4H), 8.94 (s, 0.6H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 - -156.1 (m, 2F), -138.0 - -137.9 (m, 2F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{28}H_{32}N_5O_2F_4S$, 578.2213; found, 578.2208. Anal. Calcd for $C_{28}H_{31}N_5O_2SF_4$: C, 58.22; H, 5.41; N, 12.12. Found: C, 58.05; H, 5.63; N, 11.86.

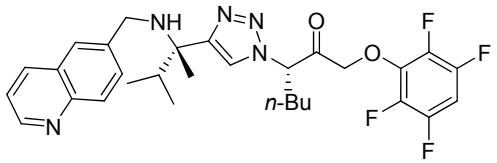
Synthesis of Diastereomerically Pure Aryloxymethyl Ketone Inhibitor 1.65 (Scheme 1.6)



Aryloxymethyl alcohol azide 1.63. This procedure was adapted from a prior publication.[41] To a 0.1 M solution of aryloxymethyl ketone azide **1.54c** (0.051 g, 0.16 mmol) in 95:5 THF:H_2O (1.6 mL) at 0 ºC was added sodium borohydride (0.008 g, 0.21 mmol). The reaction mixture was warmed to room temperature and stirred for 45 min. It was then neutralized with aqueous 1N HCl and extracted with EtOAc (3 x 5 mL). The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was taken on to the next step without purification as a 0.6:0.4 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91-0.97 (m, 3H), 1.33-1.63 (m, 4H), 1.69-1.78 (m, 2H), 2.36 (d, 0.6H, J = 4.5), 2.54 (d, 0.4H, J = 4.5), 3.45-3.50 (m, 0.6H), 3.52-3.58 (m, 0.4H), 3.91-4.02 (m, 1H), 4.22-4.31 (m, 1.6H), 4.34-4.39 (m, 0.4H), 6.78-6.86 (m, 1H). HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{13}H_{15}N_3O_2F_4Li$, 328.1254; found, 328.1260.



Aryloxymethyl alcohol 1.64. Procedure E was followed using propargyl amine **1.46** (0.020 g, 0.078 mmol), azide **1.63** (0.025 g, 0.078 mmol), sodium ascorbate (0.078 mL, 0.078 mmol), copper(II) sulfate pentahydrate (0.026 mL, 0.0078 mmol) in 1:1 *t*BuOH:H_2O (0.31 mL). The crude reaction mixture was purified by column chromatography (50-80% EtOAc/hexanes) to afford 30.0 mg (67%) of a 0.6:0.4 mixture of diastereomers of **1.64** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, 3H, J = 7.2), 0.86-0.94 (m, 3H), 1.02-1.07 (m, 3H), 1.28-1.45 (m, 4H), 1.52 (s, 3H), 1.68 (br s, 1H), 2.03-2.33 (m, 3H), 3.20-3.26 (m, 0.4H), 3.43-3.51 (m, 0.6H), 3.56-3.63 (m, 1H), 3.74-3.85 (m, 1.6H), 3.97-4.05 (m, 1H), 4.20-4.26 (m, 0.4H), 4.36-4.46 (m, 1H), 4.65-4.72 (m, 0.4H), 4.78-4.85 (m, 0.6H), 6.76-6.85 (m, 1H), 7.41 (dd, 1H, J = 4.0, 8.0), 7.53 (s, 0.4H), 7.60 (s, 0.6H), 7.67-7.73 (m, 1H), 7.76 (s, 1H), 8.06 (d, 1H, J = 8.4), 8.15 (d, 1H, J = 8.0), 8.90 (dd, 1H, J = 1.6, 4.0). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{30}H_{36}N_5O_2F_4$, 574.2795; found, 574.2805.



Aryloxymethyl ketone inhibitor 1.65. The same procedure as for aldehyde **1.71a** was followed using aryloxymethyl alcohol **1.65** (0.016 g, 0.028 mmol), Dess-Martin periodinane (0.035 g, 0.084 mmol) in water-saturated CH_2Cl_2 (0.7 mL) to afford 12.0 mg (75%) of **1.65** as a

single diastereomer as a clear oil. Chromatography resulted in racemization, thus the product was taken on to the racemization study without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (t, 3H, *J* = 7.0), 0.87 (t, 3H, *J* = 7.0), 1.01 (d, 3H, *J* = 7.0), 1.11-1.43 (m, 4H), 1.51 (s, 3H), 2.03-2.12 (m, 1H), 2.19 (sept, 1H, *J* = 7.0), 2.26-2.35 (m, 1H), 3.58 (d, 1H, *J* = 13.0), 3.77 (d, 1H, *J* = 13.0), 4.92 (s, 2H), 5.66 (dd, 1H, *J* = 5.0, 10.0), 7.17 (tt, 1H, *J* = 7.0, 10.0), 7.37 (dd, 1H, *J* = 4.0, 8.0), 7.58 (s, 1H), 7.68 (dd, 1H, *J* = 2.0, 8.5), 7.73 (s, 1H), 8.03 (d, 1H, *J* = 8.5), 8.12 (d, 1H, *J* = 8.0), 8.86 (dd, 1H, *J* = 1.5, 4.0).

Racemization study (Scheme 1.7). Diastereomerically pure inhibitor **1.65** (0.012 mg, 0.021 mmol) was dissolved in DMSO-d_6 (10.0 mL) and added to assay buffer (200 mL) consisting of a 100 mM solution of pH 6.3 sodium phosphate buffer with 400 mM of sodium chloride. The mixture was heated to 37 ºC and stirred for 3 hours. The aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 and washed with water. The aqueous layer was backextracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford an oil. ^{1}H-NMR of the crude inhibitor indicated a 1:1 mixture of diastereomers.

Assay Procedures

General assay methods. Cbz-Phe-Arg-AMC was purchased from Bachem (Torrance, CA). The proteolytic cleavage of N-acyl aminocoumarins by cruzain was conducted in Dynatech Microfluor fluorescnece 96-well microtiter plates, and readings were taken on a Molecular Devices Spectra Max Gemini SX instrument. The excitation wavelength was 370 nm and the emission wavelength was 455 nm, with a cutoff of 435 nm for AMCA substrates; the excitation wavelength was 350 nm and the emission wavelength was 450 nm, with a cutoff of 435 nm for peptidyl-AMC substrates. The assay buffer for the cruzain assays consisted of a 100 mM solution of pH 6.3 sodium phosphate buffer with 400 mM of sodium chloride, 5 mM of DTT, 10 mM of EDTA, and 0.025% Triton-X 100.

Assay procedure for AMCA substrates. Assays were conducted at 37 °C in duplicate with and without the enzyme. In each well was placed 38 μL of enzyme solution and 2 μL of a DMSO substrate solution. Assays were performed at substrate concentrations that were at minimum 6-times less than the K_m for that substrate. Relative fluorescent units (RFU) were measured at regular intervals over a period of time (maximum 15 min). A plot of RFU versus time was made for each substrate with and without cruzain. The slope of the plotted line gave relative k_{cat}/K_m of each substrate for cruzain.

Assay procedures for inhibitors. The dissociation constants (K_i and IC_{50}) for the inhibitors were calculated by the method of Dixon.[42] The concentration of cruzain in the assays was 0.25 nM and the concentration of Cbz-Phe-Arg-AMC was 0.2 μM. Assays were conducted in duplicate with and without inhibitor at five inhibitor concentrations to provide 10-90% enzyme inhibition. In each well was placed 180 μL of enzyme solution and 10 μL of a DMSO inhibitor solution. The resulting solutions were incubated for 5 min at 37 °C, and then 10 μL of the Cbz-Phe-Arg-AMC substrate was added and generation of AMC was monitored over 5 min.

The IC_{50} determinations against cathepsins S, K, L, and B were performed using the enzyme and substrate concentrations previously reported.[12]

The k_{inact}/K_i for inhibitors were determined under pseudo-first order conditions using the progress curve method.[25] Assay wells contained a mixture of inhibitor and 0.5 μM Cbz-Phe-Arg-AMC (K_m = 1.1 μM) in buffer. Aliquots of cruzain were added to each well to initiate the assay. The final enzyme concentration was 0.1 nM. Hydrolysis of the AMC substrate was monitored fluorometrically for 45 min. To determine the inhibition parameters, time points for which the control ([I] = 0) was linear were used. For each inhibitor, a k_{obs} was calculated for at least four different concentrations of inhibitors via a nonlinear regression of the data according to the equation $P = (v_i/k_{obs})[1-\exp(-k_{obs}t)$ (where product formation = P, initial rate = v_i, time = t, and the first-order rate constant = k_{obs}). If k_{obs} varied linearly with [I], then the association constant k_{ass} was determined by linear regression analysis using $k_{obs} = (k_{ass}[I])/(1+[S]/K_m)$ where [S] is the concentration of the substrate. If k_{obs} varied hyperbolically with [I], then non-linear regression analysis was performed to determine k_{inact}/K_i using $k_{obs} = k_{inact}[I]/([I]+K_i*(1+[S]/K_m))$. Inhibition was measured in quadruplicate and the average of four assays is reported.

***T. cruzi* culture assay.** Mammalian cells were cultured in RPMI-1640 medium supplemented with 5% heat-inactivated fetal calf serum (FCS) at 37 °C in 5% CO_2. The Y strain of *T. cruzi* was maintained by serial passage in bovine embryo skeletal muscle (BESM) cells. Infectious trypomastigotes were collected from culture supernatants. For inhibitor assays, J774 macrophages were irradiated (9000 rad) and plated onto twelve-well tissue culture plates 24 h prior to infection with about 10^5 trypomastigotes/well. Parasites were removed 2 h postinfection, and the medium was supplemented with the appropriate cysteine protease inhibitor (10 μM) (n=3 per treatment). For inhibitors **1.57, 1.58, 1.59**, and **1.62** the concentration was lowered to 5 μM on days 9, 7, 12, and 12, respectively. Treatment was ended on day 14 for inhibitors **1.57-1.59**. Inhibitor stocks (20 mM) in DMSO were stored at 4 °C. Fresh RPMI medium with or without inhibitor was replaced every 48 h. Monolayers were treated for 27 days and maintained without inhibitor for up to 40 days. Cultures were monitored daily by contrast phase microscopy. Untreated J774 monolayers were used as a negative control. Monolayers treated the trypanocidal inhibitor, 10 μM *N*-methyl piperazine-Phe-homoPhe-vinyl sulfone phenyl (*N*-Pip-F-hF-VSPh), acted as a positive control.[4] *T. cruzi* completed the intracellular cycle in 5 days in untreated controls but was unable to survive in macrophages treated with *N*-Pip-F-hF-VSPh (40 days). The comparative effectiveness of each inhibitor was estimated from plots of the duration of the intracellular cycle of *T. cruzi* (days) in treated vs untreated control wells.

Mouse plasma stability study. This study was performed by ADMETRx (www.admetrx.com). Carbamazepine was obtained from Sigma-Aldrich. Mouse plasma stocks were obtained from Innovative Research, Inc. (lot #K71953).

Aliquots of a 10 mM DMSO stock of **1.61** were diluted into acetonitrile and then into mouse plasma. Final experimental solute concentrations were 1 μM (0.6% acetonitrile, 0.01% DMSO). The resulting mixture was incubated at 37 ºC for 0, 5, 10, 30, or 60 minutes and quenched with acetonitrile containing 2 μM carbamazepine (internal standard), centrifuged and supernatant analyzed by LC/MS for remaining inhibitor. Analysis was performed on a Waters X-BridgeC18 50 x 2.1 mm column with 3.5 micron particle packing (186003021) at a flow rate of 1mL/min and with the temperature maintained at 50 ºC. Solvent A was water with 0.1% formic acid. Solvent B was acetonitrile with 0.07% formic acid.

The gradient timetable was as follows:

Time	%A	%B	
0.00	95	5	
1.50	5	95	via linear ramp
2.20	5	95	
2.30	95	5	

The HPLC instrument was a Waters Alliance 2795. The mass spectrometer was a Waters Quattro Premier and the MS/MS transitions monitored were:

Compound	Transition	Dwell	Cone Voltage	Collision Energy	Retention Time	
1.61	572.10 > 158.14	.075	45	35	1.12	ES+
1.61-hydrate	590.10 > 432.00	.075	20	13	1.05	ES+

Duplicate incubations were run and results are reported as percent of parent compound remaining and used to calculate half-life.

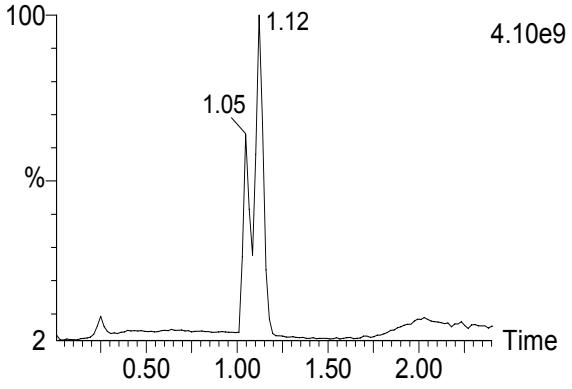


Figure 1.7. HPLC trace of inhibitor **1.61.**

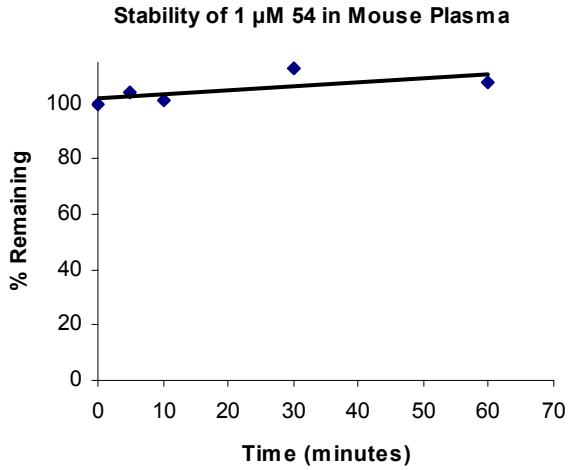


Figure 1.8. Plasma stability of inhibitor **1.61**

Efficacy studies in mice. Female C3H mice (Jax) (mean weight 22 g; n = 8) were inoculated by intraperitoneal (i.p.) injection with $1.2x10^6$ *T. cruzi* tissue culture trypomastigotes resuspended in 100 µL of RPMI medium with 5% heat inactivated horse serum. Treatment (n = 5) was initiated 24 h post infection. A control group (n = 3) of similarly infected animals was left untreated. Compound **1.61** was resuspended daily in 100 µL of 70% DMSO: 30% ddH_2O, and injected BID via i.p. for 27 days at a dose of 20 mg/kg weight. Animals were sacrificed 77 days post-infection. Heart, skeletal muscle, liver, spleen, and colon were collected for histopathological studies. Blood (50 µL) was collected by heart puncture and cultured in BHT medium at 27 ^oC. Hemocultures were maintained for 90 days and observed weekly for live parasites by contrast phase microscopy. Detailed histopathology and hemoculture results are listed in Table 1.11.

Table 1.11. Detailed histopathology and hemoculture results

entry	treatment	tissue type	infection/inflammation[a]	hemoculture
1	none	heart	N, mild i/i	positive
		skeletal muscle	+A, moderate i/i, necrosis	
		liver	N	
		spleen	N	
		colon	N	
2	none	heart	focal i/i	positive
		skeletal muscle	moderate i/i	
		liver	N	
		spleen	N	
		colon	N	
3	none	heart	+A, moderate i/i	positive
		skeletal muscle	+A, moderate i/i, focal necrosis	
		liver	N	
		spleen	N	
		colon	N	
4	20 mg/kg/BID of **1.61** via ip	heart	N	negative
		skeletal muscle	moderate i/i	
		liver	N	
		spleen	N	
		colon	N	
5	20 mg/kg/BID of **1.61** via ip	heart	N	positive
		skeletal muscle	+A, moderate i/i	
		liver	N	
		spleen	N	
		colon	N	
6	20 mg/kg/BID of **1.61** via ip	heart	necrotic myocardiocytes	negative
		skeletal muscle	+++A, moderate i/i	
		liver	N	
		spleen	N	
		colon	N	
7	20 mg/kg/BID of **1.61** via ip	heart	N, mild i/i	not determined
		skeletal muscle	++A, intense i/i	
		liver	N	
		spleen	N	
		colon	N	
8	20 mg/kg/BID of **1.61** via ip	heart	N, mild focal i/i	positive
		skeletal muscle	intense i/i and necrosis	
		liver	N	
		spleen	N	
		colon	N	

[a] N, normal tissue; i/i: focal, mild, moderate, intense; A, *T. cruzi* amastigotes.

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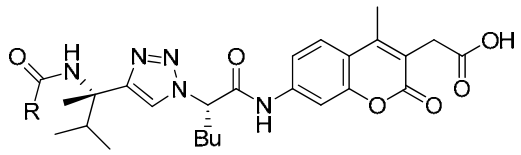
Appendix 1.1. Cleavage Efficiencies of 1,2,3-Triazole Substrates Against Cruzain

Table A1.1.1. Relative Cleavage Efficiencies of 1,2,3-Triazole Amide Substrates Against Cruzain



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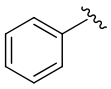
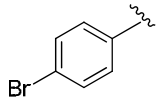
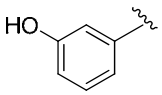
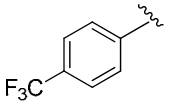
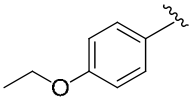
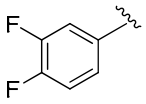
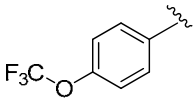
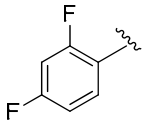
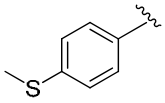
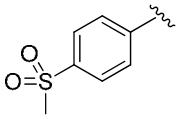
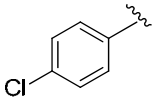
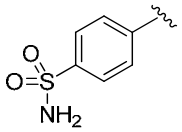
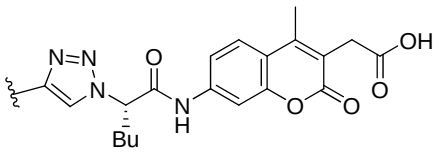
1		1.0	7		1.6
2		0.1	8		2.3
3		2.4	9		1.3
4		4.9	10		0.6
5		4.6	11		3.1
6		0	12		2.9

Table A1.1.2. Relative Cleavage Efficiencies of 1,2,3-Triazole Alcohol Substrates with Varying P2 Substituents Against Cruzain



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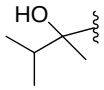
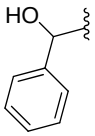
1		100	9		1
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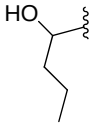
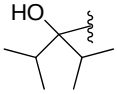
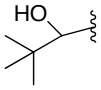
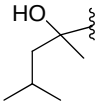
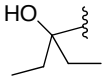
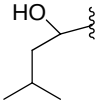
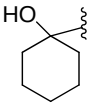
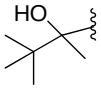
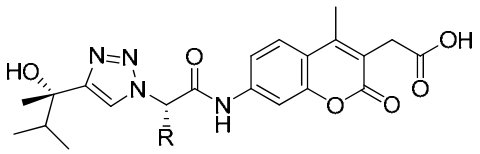
3		10	11		46
4		12	12		20
5		42	13		130
6		35	14		22
7		25	15		46
8		15			

Table A1.1.3. Relative Cleavage Efficiencies of 1,2,3-Triazole Alcohol Substrates with Varying P1 Substituents Against Cruzain



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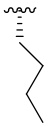
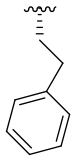
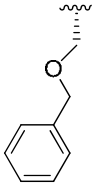
		1.0
		0.6
		0.5

Chapter 2. Structure-Based Design, Synthesis, and Cell-culture Evaluation of Second-Generation Nonpeptidic Tetrafluorophenoxymethyl Ketone Cruzain Inhibitors.

Nonpeptidic tetrafluorophenoxymethyl ketone inhibitors were found to be a promising class of cruzain inhibitors (Brak, K.; Doyle, P. S.; McKerrow, J. H.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6404-6410) [Chapter 1]. *A high-resolution crystal structure confirmed the mode of inhibition and revealed key binding interactions of this novel inhibitor class. Subsequent structure-guided optimization then resulted in inhibitor analogs with improvements in potency despite minimal or no additions in molecular weight. Evaluation of the analogs in cell culture showed enhanced activity. The majority of this work was published as a full paper* (Brak, K.; Kerr, I. D.; Barrett, K. T.; Fuchi, N.; Debnath, M.; Ang, K.; Engel, J. C.; McKerrow, J. H; Doyle, P. S.; Brinen, L. S.; Ellman, J. A. *J. Med. Chem.* **2010**, 53, 1763-1773).

Authorship

This work was conducted in collaboration with Kim Barrett, Dr. Nobuhiro Fuchi, Dr. Iain Kerr, Dr. Moumita Debnath, Prof. Linda Brinen, Dr. Kenny Ang, Dr. Juan Engel, Dr. Patricia Doyle, and Prof. James McKerrow. Kim and Dr. Fuchi assisted in the synthesis of inhibitor analogs **2.4a-j**. The co-crystal structure of cruzain•**2.2** was obtained by Dr. Kerr and Dr. Debnath at the University of California, San Francisco. Dr. Ang and Dr. Engel developed the high-throughput screen and performed the cell culture studies of inhibitor analogs **2.4a-j** at the Sandler Center for Basic Research in Parasitic Diseases at the University of California, San Francisco.

Introduction

Chagas disease, also known as American Trypanosomiasis, results from infection by the *Trypanosoma cruzi* (*T. cruzi*) parasite. It is estimated that 15 million people are infected with the parasite, resulting in more than 12,000 deaths each year.[1] Chagas disease is the leading cause of cardiomyopathy in Latin America.[2] Current treatment consists of nitroaromatic drugs that are not only toxic but also ineffective for the chronic stage of the disease.[3] These limitations of the existing drugs along with emerging resistance have provided considerable impetus for the development of novel chemotherapy for Chagas disease.[4] One approach consists of developing inhibitors of cruzain, the primary cysteine protease expressed by *T. cruzi* during infection.[5] Cruzain, a cysteine protease of the papain-like family, plays a vital role at every stage of the parasite's life cycle; it is involved in protein degradation for nutrition, host cell remodeling, and evasion of host defense mechanisms.[6]

Vinyl sulfone **2.1**, a peptidic irreversible inhibitor of cruzain, has been shown to cure parasitic infections in both cell and animal models (Figure 2.1).[7] While inhibitor **2.1** is effective, it is peptidic and consequently exhibits low oral bioavailability and a short circulating half-life.[8,9] With this in mind, we recently applied the substrate activity screening method to cruzain to obtain novel and potent entirely nonpeptidic inhibitors.[10,11] In particular, the 1,2,3-triazole-based tetrafluorophenoxymethyl ketone irreversible inhibitor **2.2** was found to completely eradicate the *T. cruzi* parasite in cell culture (Figure 2.1). In addition to the nonpeptidic nature of inhibitor **2.2**, the tetrafluorophenoxymethyl ketone functionality represents a very promising mechanism-based pharmacophore due to its high selectivity for cysteine protease inhibition,[12,13] as well as the lack of toxicity in animal studies, which was established for a tetrafluorophenoxymethyl ketone-based caspase inhibitor that has entered Phase II clinical trials.[14]

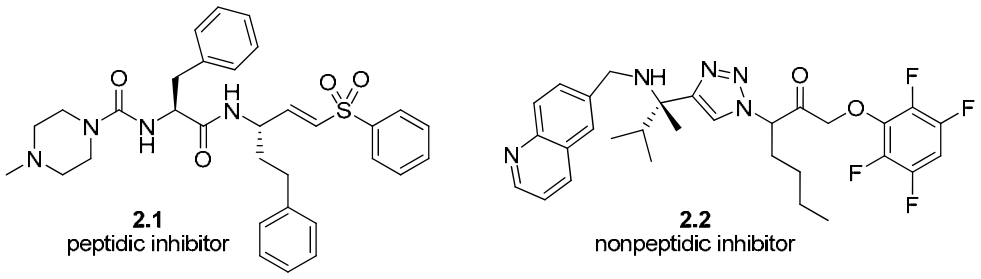


Figure 2.1. Structures of potent irreversible cruzain inhibitors: dipeptidyl vinyl sulfone **2.1** and 1,2,3-triazole-based tetrafluorophenoxymethyl ketone **2.2**.

Herein we report a high resolution X-ray crystal structure of **2.2** complexed to cruzain. This structural information provided characterization of the binding mode of **2.2** and enabled the design of inhibitors that are approximately 4-fold more potent than **2.2** in addition to having more desirable physicochemical properties. The nonpeptidic nature of these compounds, coupled with their efficacy in cell-culture and mice, makes this class of inhibitors promising candidates for improved chemotherapy for Chagas disease.

X-ray Crystal Structure of a 1,2,3-Triazole Inhibitor Complexed to Cruzain

*Structural Insight Provided by the Crystal Structure of Cruzain•**2.2***

The X-ray crystal structure of **2.2** complexed to cruzain verified both the mode of binding and inactivation (PDB ID 3IUT). Inhibitor **2.2** is bound in the general orientation that was previously predicted by superimposition with a structure of the homologous protein cathepsin S in complex with a triazole inhibitor that is structurally similar to **2.2** (PDB ID 2H7J).[10,15] In particular, the *n*-butyl group is located in the S1 subsite, the methyl and isopropyl functionalities in the S2 subsite, and the quinoline ring in the S3 subsite (Figure 2.2).

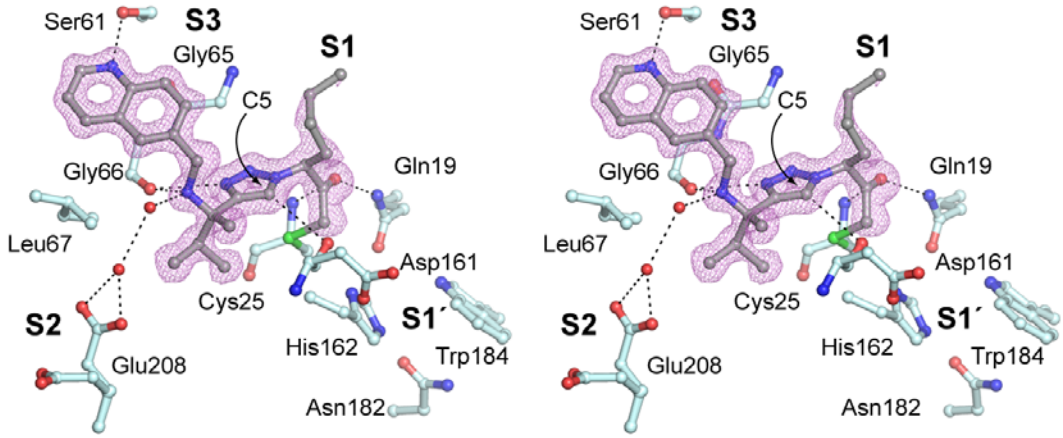


Figure 2.2. Crystal structure of the cruzain•**2.2** complex (PDB ID 3IUT) elucidates the binding mode of **2.2** in the cruzain substrate-binding site. Cruzain residues are colored pale cyan and the inhibitor is colored grey. The unbiased mFo-DFc electron density for the inhibitor is shown in violet, contoured at the 3σ level. Black dashed lines indicate hydrogen bond interactions between inhibitor **2.2** and amino acid residues in cruzain's catalytic pocket. The C(5) of the 1,2,3-triazole ring is labeled.

The specific binding interactions between cruzain and inhibitor **2.2** were elucidated by the high-resolution X-ray crystal structure of cruzain•**2.2**. While aryloxymethyl ketone inhibitors are well-studied as caspase inhibitors,[16,17] this pharmacophore has not been structurally visualized for cruzain nor any members of the papain superfamily. The proposed mechanism of inhibition of cysteine proteases by activated ketones involves nucleophilic attack of the cysteine thiolate on the carbonyl carbon leading to the formation of a thiohemiketal stabilized by the oxyanion hole (Figure 2.3).[13,17] Breakdown of the tetrahedral intermediate then results in a displacement of the leaving group and hence irreversible inhibition. The crystal structure reveals

that the thiol nucleophile of the active site Cys25 has effectively displaced the tetrafluorophenoxy moiety of the inhibitor. Taking into account the high resolution of the data, there was no need to include a specific restraint on the C•Sγ distance, while ensuring overall good geometry for the model. As a result, the distance refines to 1.83Å, indicating the formation of a covalent bond between Cys25 and the inhibitor. The pharmacophore is further stabilized in the S1′ subsite through the formation of hydrogen bonds with the peptide amide of Cys25 (3.13Å) and Nε2 of Gln19 (3.13Å) (Figure 2.2).

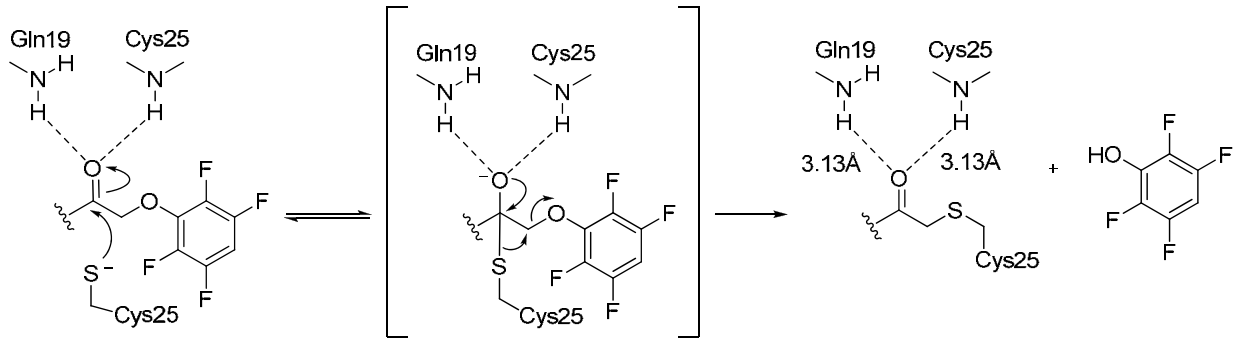


Figure 2.3. The proposed mechanism of inhibition for tetrafluorophenoxymethyl ketone inhibitor **2.2**.

A common feature of cruzain-small molecule structures is hydrogen bonding with Gly66, stabilizing the inhibitor in the substrate-binding cleft.[18-20] In the cruzain•**2.2** complex, Gly66 forms a hydrogen bond with both the amine functionality of the inhibitor (2.85Å) and the N(3) atom of the 1,2,3-triazole of the inhibitor (3.20Å) (Figure 2.2). The strong dipole moment of 1,2,3-triazole rings polarize the C(5) proton to such a degree that it can function as a hydrogen-bond donor.[21] Indeed, the hydrogen bond commonly observed with the backbone carbonyl of Asp161 and amide protons of small molecules is also observed with the C(5) proton of the triazole of inhibitor **2.2** (3.41Å) (Figure 2.2). Due to the ability of 1,2,3-triazoles to function as rigid linking units that mimic the atom placement and electronic properties of a peptide bond without the susceptibility of hydrolysis, many known 1,2,3-triazoles possess biological activity.[22]

Prior development of this inhibitor class focused on optimizations of interactions in the S3 subsite.[10] Planar heterocycles were introduced to provide hydrophobic interactions with the hydrophobic residues of the pocket. Nitrogen or oxygen heteroatoms were also positioned in the heterocyle to take advantage of potential hydrogen-bonding interactions with the serine residue present in the S3 pocket. A quinoline substituent was found to provide the greatest binding affinity. The crystal structure illustrates that efficient binding is aided by the formation of a hydrogen bond between the quinoline nitrogen and Ser61 (2.79Å), in addition to nonpolar interactions of the quinoline with Gly65 and Leu67 in the S3 subsite (Figure 2.2). Additional nonpolar interactions also contribute towards binding, with the isopropyl moiety stabilized by Leu67, and the P2 methyl substituent stabilized by nonpolar regions of Asp161 oriented toward the inhibitor.

The residue at the bottom of the S2 subsite is of particular interest as it is crucial in determining the substrate specificity of papain family cysteine proteases.[20] With flexible Glu208 at this position, cruzain has evolved an S2 subsite that is able to tolerate both basic and hydrophobic residues. An interesting feature of the cruzain•**2.2** crystal structure is the dual

conformation of Glu208. In the crystallized complex, one conformer points towards the inhibitor and interacts with the amine functionality via two bridging water molecules (Figure 2.2). A second conformer adopts a solvent-exposed orientation, pointing out of the S2 subsite and into a nearby solvent channel in the crystal. We were surprised to discover that the latter appears to interact with a transient and low occupancy second copy of **2.2** in a solvent channel of the crystal (Figure 2.4). As the occupancy of the atoms appear low (only the N-terminal portion is partially visible) and we were unable to unequivocally assign atomic positions for all atoms in the molecule, we have not included this second inhibitor molecule in the final coordinates. Of import for this study, while polar interactions with residues lining the solvent channel are possible with this second molecule copy, there is no evidence of covalent bond formation with the pharmacophore, in sharp contrast to what is experimentally observed in the active site bound copy of **2.2**.

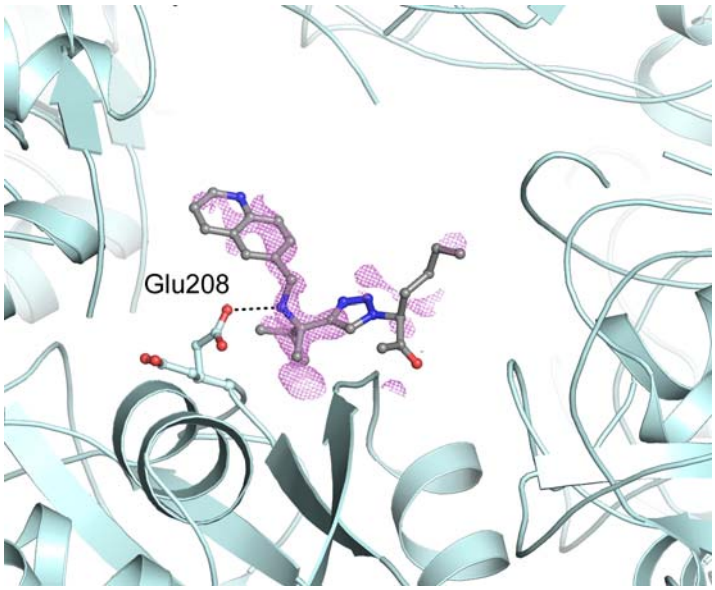


Figure 2.4. The putative position of a second inhibitor **2.2** molecule, bound at low occupancy in a solvent channel. Cruzain is colored pale cyan and the inhibitor grey. The unbiased mFo-DFc electron density for the inhibitor is shown in violet, contoured at the 3σ level.

The stereocenter alpha to the aryloxymethyl ketone moiety is configurationally unstable with complete racemization within three hours under the assay conditions (pH = 6.3, 37 ºC).[10] The P1 *n*-butyl substituent is less ordered than the rest of the inhibitor and, accordingly, the B-factors in this region are higher in comparison to the rest of the small molecule. However, the crystal structure clearly establishes binding of the epimer with the *S*-configuration at the alpha stereocenter (Figure 2.2).

Comparison of Cruzain•Nonpeptidic Inhibitor Structures

Our collaborators, Linda Brinen and Iain Kerr, recently determined the first crystal structure of a nonpeptidic cruzain inhibitor, **2.3**, complexed to cruzain (PDB ID 3HD3).[23] Least-squares superimposition with the cruzain•**2.2** complex matches 215 Cα positions with root mean square distances (rmsd) of 0.36Å (3HD3, monomer A) and 214 Cα positions with root mean

square distances (rmsd) of 0.42Å (3HD3, monomer B). Inhibitor **2.3** is a moderately potent cruzain inhibitor (k_{inact}/K_i = 6,020 ± 820 $s^{-1}M^{-1}$) that carries the well-characterized vinyl sulfone warhead at the P1′ position (Figure 2.5a). Irreversible inhibition of cruzain is achieved by a Michael addition of the active site thiolate to the β-carbon of the unsaturated vinyl group of the inhibitor. The P2 and P3 substituents (cyclohexane and chlorophenyl, respectively) differ in comparison with **2.2**; however, both inhibitors are capable of establishing nonpolar interactions at these positions with residues lining the binding sites. Interestingly, both inhibitors share the *n*-butyl group at the P1 position and while this moiety is more flexible than the other substituents in **2.2**, the *n*-butyl moiety in **2.3** is well-ordered and unambiguous in the electron density.

Superimposition of the two models shows that inhibitor **2.2** is able to form polar interactions missing in the complex with vinyl sulfone **2.3**; specifically, the amine-Gly66 and quinoline-Ser61 hydrogen bonds as well as the amine-Glu208 indirect interaction through two bridging water molecules (Figure 2.5b). The favorable binding resulting from these interactions is likely the reason for the greater potency of inhibitor **2.2** (k_{inact}/K_i = 157,000 ± 20,000 $s^{-1}M^{-1}$)**.** The amide of inhibitor **2.3** forms a hydrogen bond with the backbone carbonyl of Asp161, an interaction that is replaced in **2.2** by the C(5) hydrogen of the 1,2,3-triazole ring. With vinyl sulfone **2.3** lying deeper in the substrate-binding cleft, the *n*-butyl group is able to form nonpolar contacts with Gly23 that are not present in **2.2**. Therefore, long alkyl functionalities at P1 may not be desirable for the aryloxymethyl ketone cruzain inhibitors. Indeed, only a modest reduction in k_{inact}/K_i is seen when the *n*-butyl is replaced by an ethyl in **2.4a** (Table 2.1) (vide infra), suggesting that the additional two atoms do not contribute appreciably to inhibitor potency.

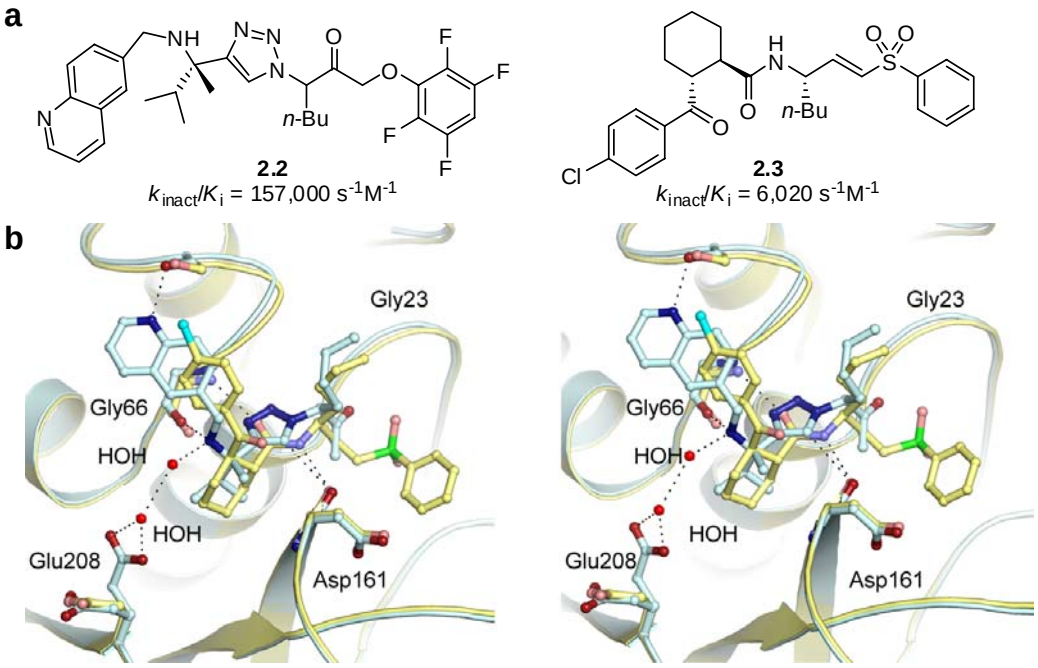


Figure 2.5. Structural comparison of nonpeptidic inhibitors **2.2** and **2.3**. (**a**) Chemical structures and second-order inactivation constants of tetrafluorophenoxymethyl ketone inhibitor **2.2** and vinyl sulfone inhibitor **2.3**. (**b**) A superimposition of cruzain•**2.2** (PDB ID 3IUT) and cruzain•**2.3** (PDB ID 3HD3) crystal structures. The cruzain•**2.2** complex is colored pale cyan, while the cruzain•**2.3** complex is colored yellow. Black dashed lines indicate hydrogen bond interactions between the inhibitors and amino acid residues in cruzain's catalytic pocket.

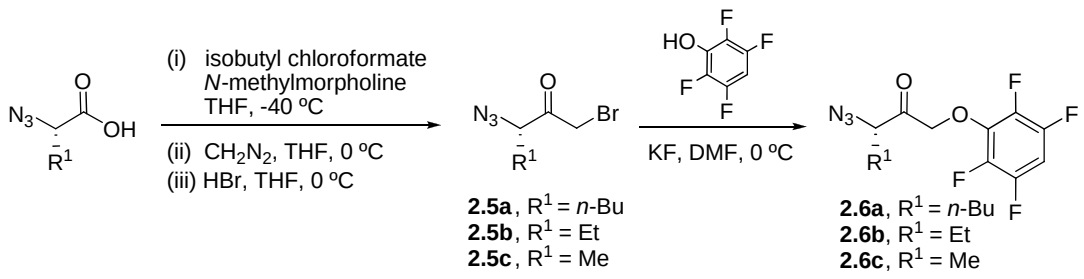
Structure-Guided Design of Inhibitor Analogs

Synthesis of Tetrafluorophenoxymethyl Ketone Inhibitor Analogs

The synthesis of 1,2,3-triazole-based tetrafluorophenoxymethyl ketone cruzain inhibitor analogs **2.4a-j** with differing R1 and R2 substituents required the preparation of various aryloxymethyl ketone azide and quinoline propargyl amine intermediates (Scheme 2.1). The bromomethyl ketone azides **2.5a-c** were obtained via a three-step, one-pot procedure from the corresponding azido acids by preparation of the isobutyl mixed anhydride, addition of diazomethane to form a diazomethyl ketone, and final treatment with hydrobromic acid. Displacement of the bromide by 2,3,5,6-tetrafluorophenol afforded aryloxymethyl ketone azide intermediates **2.6a-c** (Scheme 2.1a). Enantiomerically pure propargyl amine intermediates **2.8a-g** were prepared by a two step reductive amination of quinoline-6-carboxyaldehyde with tertiary carbinamines **2.7a-g** (Scheme 2.1b). 1,4-Disubstituted-1,2,3-triazole inhibitor analogs **2.4a-i** were then synthesized via a regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition (Scheme 2.1c). Formation of the triazole in the final step enabled the rapid synthesis of a variety of inhibitors resulting from various combinations of the azide and alkyne intermediates.

Scheme 2.1. Synthesis of 1,4-disubstituted-1,2,3-triazole cruzain inhibitor analogs

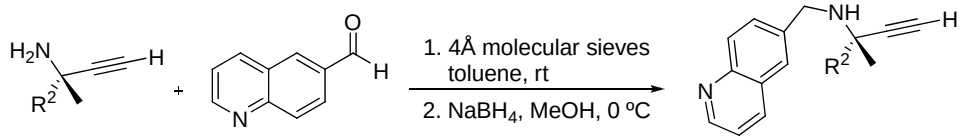
a



2.5a, R^1 = *n*-Bu
2.5b, R^1 = Et
2.5c, R^1 = Me

2.6a, R^1 = *n*-Bu
2.6b, R^1 = Et
2.6c, R^1 = Me

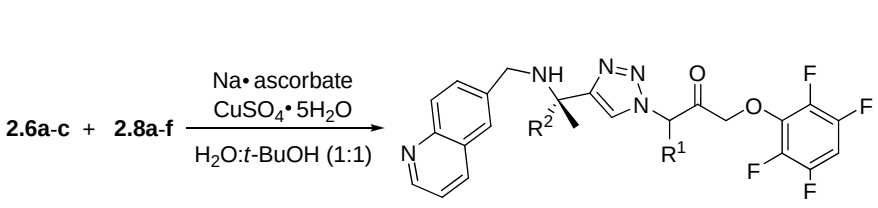
b



2.7a, R^2 = *i*-Pr
2.7b, R^2 = *cyclo*-Pr
2.7c, R^2 = *i*-Bu
2.7d, R^2 = *cyclo*-Bu
2.7e, R^2 = *cyclo*-Pent
2.7f , R^2 = 2-furan
2.7g, R^2 = *cyclo*-Hex

2.8a, R^2 = *i*-Pr
2.8b, R^2 = *cyclo*-Pr
2.8c, R^2 = *i*-Bu
2.8d, R^2 = *cyclo*-Bu
2.8e, R^2 = *cyclo*-Pent
2.8f , R^2 = 2-furan
2.8g, R^2 = *cyclo*-Hex

c



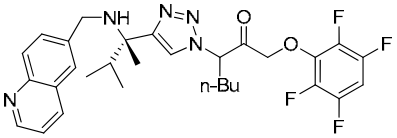
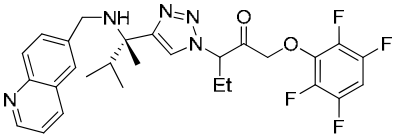
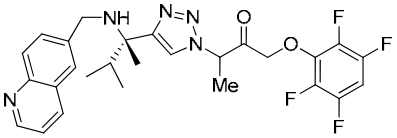
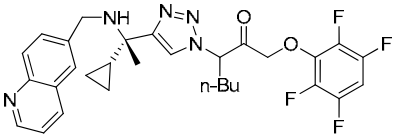
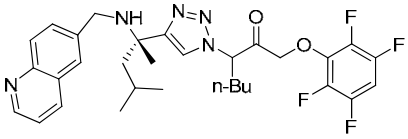
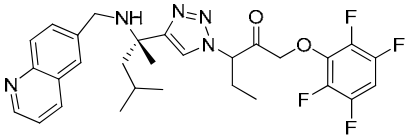
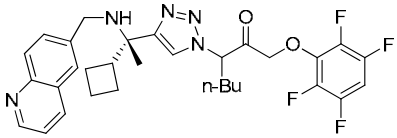
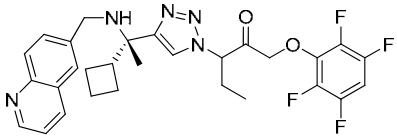
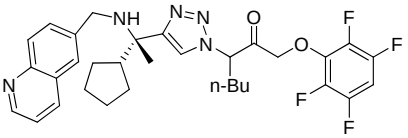
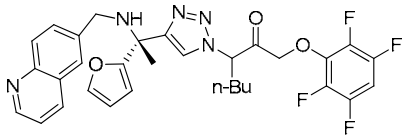
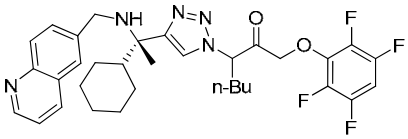
2.4a, R^1 = Et, R^2 = *i*-Pr
2.4b, R^1 = Me, R^2 = *i*-Pr
2.4c, R^1 = *n*-Bu, R^2 = *cyclo*-Pr
2.4d, R^1 = *n*-Bu, R^2 = *i*-Bu
2.4e, R^1 = Et, R^2 = *i*-Bu
2.4f , R^1 = *n*-Bu, R^2 = *cyclo*-Bu
2.4g, R^1 = Et, R^2 = *cyclo*-Bu
2.4h, R^1 = *n*-Bu, R^2 = *cyclo*-Pent
2.4i , R^1 = *n*-Bu, R^2 = 2-furan
2.4j , R^1 = *n*-Bu, R^2 = *cyclo*-Hex

Inhibition Kinetics of Tetrafluorophenoxymethyl Ketone Inhibitor Analogs

The crystal structure allowed for the design of analogs that take advantage of the specific contours of the hydrophobic regions of the S1 and S2 pockets. Numerous studies on cruzain substrates and inhibitors have established that a variety of unbranched P1 residues are accommodated because the S1 pocket is solvent-exposed and less well-defined.[19,24] As such, inhibitor analogs **2.4a** (R1 = ethyl) and **2.4b** (R1 = methyl) were synthesized to probe the relative contributions of the aliphatic *n*-butyl chain while reducing molecular weight and number of rotatable bonds of the inhibitor. While decreasing the R1 side chain to a methyl group resulted in a thirteen-fold decrease in potency, truncation to the smaller ethyl chain did not significantly affect the inhibitor potency (Table 2.1). Analysis of the separate binding constant K_i and rate constant for enzyme inactivation k_{inact} provided insight into how the structural changes are reflected in these values. The reduction in k_{inact}/K_i was largely a result of increases in the binding constant K_i with an approximate fifteen- and two-fold increase for inhibitor **2.4a** and **2.4b**, respectively. Interestingly, the ethyl derivative **2.4a** was only slightly less potent despite a two-fold decrease in binding affinity because the k_{inact} increased by almost two-fold. The other sets of *n*-butyl and ethyl analogs, **2.4d**/**2.4e** and **2.4f**/**2.4g**, displayed the same trend: the ethyl derivatives had a slightly decreased binding affinity (higher K_i) and an enhanced k_{inact} resulting in approximately the same second-order rate constants k_{inact}/K_i.

Cruzain belongs to a family of enzymes where the interaction with the S2 pocket of the enzyme is the major specificity determinant.[20] The Connolly surface of the hydrophobic S2 pocket indicated that the isopropyl substituent in inhibitor **2.2** did not entirely fill the cavity. To take full advantage of the hydrophobic S2 pocket, a series of inhibitor analogs with increasingly larger R2 substituents were prepared. Replacement of the isopropyl group with the isobutyl group in inhibitor **2.4d** and the cyclobutyl group in inhibitor **2.4f** resulted in four-fold improved potency with k_{inact}/K_i values of 657,000 $M^{-1}s^{-1}$ and 680,000 $M^{-1}s^{-1}$, respectively (Table 2.1). Not surprisingly, the increase in k_{inact}/K_i was a direct result of a four-fold increase in the binding affinity (lower K_i) of these inhibitors for cruzain while the k_{inact} remained the same. Interestingly, inhibitor **2.4h** with a cyclopentyl substituent had a slightly lower k_{inact}/K_i due to a slight decrease in k_{inact}. The decrease in potency observed for inhibitor **2.4i**, which has a furan in place of the cyclopentyl is consistent with the hydrophobic nature of the S2 pocket. The cyclohexyl substituent of inhibitor **2.4j** was too large, resulting in a dramatic increase in K_i and hence drop in the overall second-order rate constant. These results are consistent with modeling studies, which indicated that the cyclobutyl and cyclopentyl ring were of optimal size, while the cyclohexyl ring was sterically hindered by close contacts with the S2 subsite. Inhibitor analogs combining optimal R1 and R2 substituents, **2.4e** (R1 = ethyl, R2 = isobutyl) and **2.4g** (R1 = ethyl, R2 = cyclobutyl), were also prepared and showed a three-fold increase in potency.

Table 2.1. Inhibition kinetics of tetrafluorophenoxymethyl ketone inhibitors against cruzain

cmpd	structure	k_{inact}/K_i ($M^{-1}s^{-1}$) [a]	K_i (μM)	k_{inact} (s^{-1})
2.2		157,000 ± 20,000	0.46 ± 0.4	0.037 ± 0.014
2.4a		124,000 ± 14,000	1.04 ± 0.45	0.066 ± 0.026
2.4b		12,300 ± 900	6.76 ± 0.99	0.043 ± 0.004
2.4c		179,000 ± 4,000	0.94 ± 0.3	0.089 ± 0.030
2.4d		657,000 ± 40,000	0.10 ± 0.03	0.036 ± 0.011
2.4e		487,000 ± 38,000	0.19 ± 0.12	0.048 ± 0.029
2.4f		680,000 ± 81,000	0.13 ± 0.06	0.047 ± 0.019
2.4g		522,000 ± 46,000	0.35 ± 0.08	0.096 ± 0.026
2.4h		432,000 ± 45,000	0.11 ± 0.03	0.025 ± 0.004
2.4i[b]		23,000 ± 3,000	1.07 ± 0.22	0.013 ± 0.001
2.4j		58,000 ± 8,000	1.22 ± 0.39	0.037 ± 0.011

[a] Kinetic assays were performed at least in triplicate (SD values included). [b] Kinetic assay was performed once.

Evaluation of a Peptidic Tetrafluorophenoxymethyl Ketone Inhibitor

We were interested in directly comparing the peptidic tetrafluorophenoxymethyl ketone inhibitor **2.5**, which contains the dipeptidyl scaffold from the potent vinyl sulfone inhibitor **2.1**, with the nonpeptidic tetrafluorophenoxymethyl ketone inhibitor **2.2** (Scheme 2.6). Evaluation of these binding scaffolds with the same pharmacophore would provide further insight into the comparative binding of nonpeptidic and peptidic cruzain inhibitors (Figure 2.6).

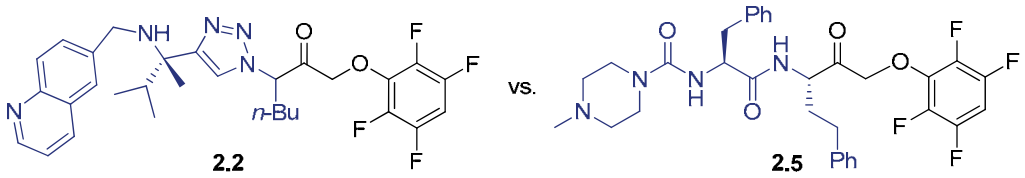
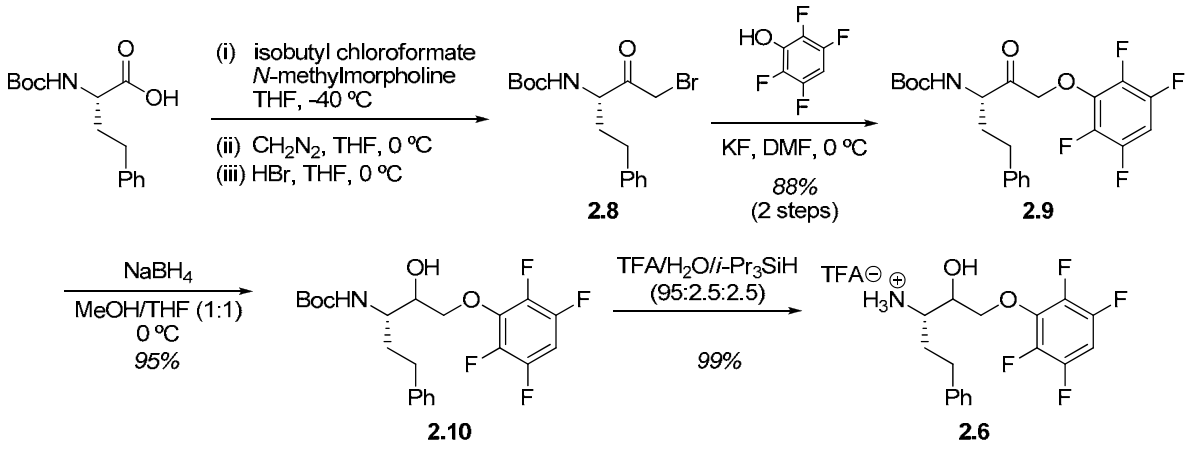


Figure 2.6. Structures of nonpeptidic and peptidic tetrafluorophenoxymethyl ketone inhibitors.

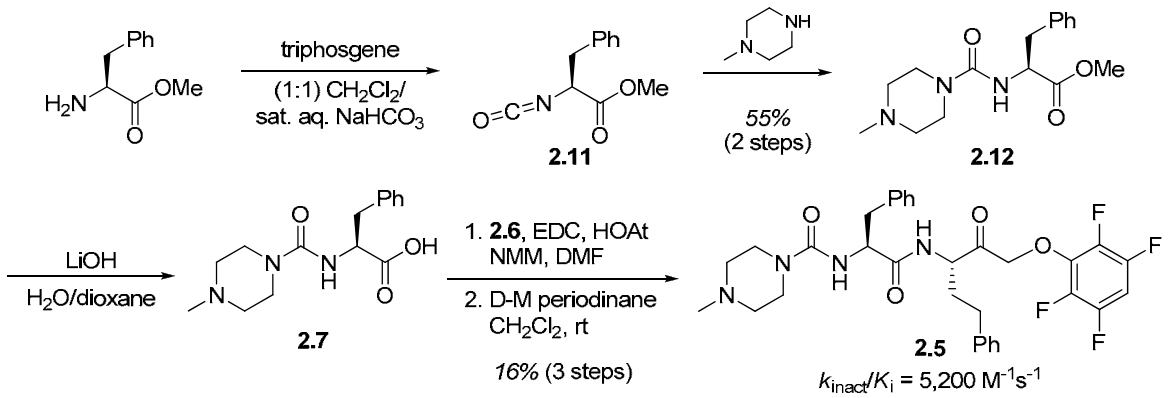
We envisioned that tetrafluorophenoxymethyl ketone inhibitor **2.5** could be accessed by the coupling of amine **2.6** and carboxylic acid **2.7**. The synthesis of amine **2.6** began by formation of bromomethyl ketone **2.8** from *N*-Boc-homophenylalanine by the same three-step, one-pot procedure previously employed (Scheme 2.2). Displacement of the bromide by tetrafluorophenol afforded aryloxymethyl ketone intermediate **2.9** in good yield. Ketone **2.9** was then reduced in order to prevent cyclization onto the electrophilic ketone in subsequent steps. Finally, deprotection of the Boc group proceeded smoothly to provide the amine trifluoroacetate salt **2.6**.

Scheme 2.2. Synthesis of amine **2.6**



The synthesis of the urea moiety of acid **2.7** was accomplished via isocyanate formation of the methyl ester of phenylalanine followed by addition of *N*-methyl piperazine and a subsequent saponification (Scheme 2.3). Acid **27** was then coupled to amine **2.6** using standard peptide coupling reagents. Oxidation of the alcohol then afforded the peptidic tetrafluorophenoxymethyl ketone inhibitor **2.5**.

Scheme 2.3. Synthesis of peptidic tetrafluorophenoxymethyl ketone inhibitor **2.5**



Kinetic analysis of inhibitor **2.5** revealed that it was only a moderate irreversible inhibitor of cruzain (k_{inact}/K_i = 5,200 $M^{-1}s^{-1}$). This result was somewhat surprising as peptidic inhibitor scaffolds, which more closely resemble the natural substrates, generally bind more efficiently to the target than nonpeptidic inhibitors. The difference in the second-order rate constants of inhibitors **2.5** and **2.2** further confirms that the orientation and/or binding of the tetrafluorophenoxy leaving group plays a significant role in determining inhibitor potency.

Cell-Culture Evaluation of Inhibitor Analogs

Tetrafluorophenoxymethyl ketone inhibitor **2.2** has previously been shown to completely eradicate the *T. cruzi* parasite in cell culture.[10] Macrophages infected with *T. cruzi* were treated for 27 days with 10 μM inhibitor **2.2** and cells were monitored for two more weeks to ensure complete elimination of the parasite. The more potent inhibitor analogs **2.4a** and **2.4c**-**h** were also evaluated for their effectiveness at eradicating the *T. cruzi* parasite in cell culture. For these analogs as well as inhibitor **2.2**, a new high throughput assay that provides IC_{50} values as well as an evaluation of compound toxicity was employed.[25] In a 96-well plate, BESM cells infected with *T. cruzi* were incubated with several concentrations of the inhibitors (0, 0.3, 1, 3, and 10 μM) for 3 days at 37 ºC. The wells were fixed and stained with a DNA fluorescent dye and then scanned with an automated fluorescence microscope. Host nuclei (>150 μm^2) and parasite kinetoplast (2-4 μm^2) were differentiated based on size. A reduction in the number of *T. cruzi* per host cell provided a measure of parasite growth inhibition and a decrease in the number of host nuclei provided a quantitative measure of cytotoxicity.

All of the inhibitor analogs tested significantly decreased the number of intracellular parasites after the 3 day period of incubation as compared to untreated controls (Table 2.2). Curiously, even though the inhibitor derivatives **2.4a**, **2.4e**, and **2.4g** with R1 = ethyl had comparable second-order inactivation rates to their *n*-butyl counterparts (Table 2.1), they did not perform as well in cell culture. This is evidenced in all three pairs of *n*-butyl/ethyl inhibitor analogs (Table 2.3: **2.2**/**2.4a**, **2.4d**/**2.4e**, and **2.4f**/**2.4g**). The more potent inhibitors **2.4d**, **2.4f**, and **2.4h** with R1 = *n*-butyl all had improved activity in cell culture (3.1-4.2 μM) compared to the first-generation inhibitor **2.2** (5.1 μM). Significantly, no apparent toxicity was observed; the host cell IC_{50} values were ≥10 μM for all of the tetrafluorophenoxymethyl ketone inhibitors.

Table 2.2. Evaluation of efficacy and toxicity of inhibitors in cell culture

cmpd	*T. cruzi* IC_{50} (μM)[b]	host IC_{50} (μM)[a,b]
2.2	5.1	> 10
2.4a	8.3	> 10
2.4c	4.3	> 10
2.4d	3.1	> 10
2.4e	5.7	> 10
2.4f	4.1	> 10
2.4g	5.8	> 10
2.4h	4.2	10

[a] *T. cruzi*-infected BESM cells. [b] Values are an average of duplicate or triplicate runs.

Conclusion

The drugs available to treat Chagas disease are decades old and limited in efficacy.[3] Validation of cruzain, the major cysteine protease of the *T. cruzi* parasite, as a target has provided an opportunity for developing improved chemotherapy.[5] Proteases are a well-studied class of enzymes due to their involvement in many cellular processes and importance as targets for small-molecule therapeutics.[26] Peptidic inhibitors, consisting of small peptides coupled to an electrophilic pharmacophore, easily mimic the natural substrates of the protease and hence result in potent inhibitors. However, they do not possess the molecular properties required for drug candidates due to their susceptibility to hydrolysis, metabolism, and rapid clearance.[9,27] To address this issue, we have developed a nonpeptidic class of triazole-based cruzain inhibitors.[10,11]

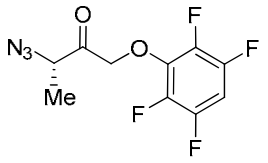
In this study, a high resolution crystal structure of tetrafluorophenoxymethyl ketone inhibitor **2.2** complexed with cruzain was obtained. The structural information revealed how the triazole moiety of the inhibitor is able to provide the same stabilizing interactions with the enzyme active site as the amide bond in peptidic inhibitors. In addition to characterizing the binding mode of inhibitor **2.2**, the structure enabled the design of inhibitors with 4-fold increases in inhibitory activity, and for select inhibitors, improved physicochemical properties such as reduced molecular weight, lower hydrophobicity, and a reduction in the number of rotatable bonds. Several of these inhibitors also showed comparable or modestly improved potency relative to **2.2** in cell culture evaluation.

The tetrafluorophenoxymethyl ketone inhibitor **2.2** and the newly designed inhibitors **2.4a-j** represent very promising drug leads for the treatment of Chagas disease. Evaluation of the pharmacokinetic properties of these compounds along with their evaluation in animal models of Chagas disease via oral administration is under active investigation.

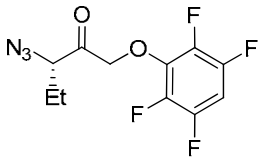
Experimental Section

General methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without purification. Tetrahydrofuran (THF), diethyl ether, methylene chloride, and toluene were obtained from a Seca Solvent Systems by GlassContour (solvent dried over alumina under an N_2 atmosphere). Anhydrous DMF (water <50 ppm) was purchased from Acros. p-Toluenesulfonylmethylnitrosamide (Diazald) was purchased from Sigma-Aldrich. (*S*)-*tert*-Butanesulfinamide was provided by AllyChem Co. Ltd (Dalian, China). Inhibitor **2.2** and intermediates **2.5a**, **2.6a**, and **2.8a** were synthesized as previously reported.[10] Propargyl amines **2.7a-g** were synthesized according to reported procedures.[28] All reactions were carried out in flame-dried glassware under an inert N_2 atmostphere. Normal-phase purification was carried out with Merck 60 230-240 mesh silica gel. Reverse-phase HPLC purification was conducted either with an Agilent 1100 series instrument or Biotage SP1 instrument (Charlotteville, VA) equipped with a Biotage C18SH column. Reverse-phase HPLC analysis was conducted with an Agilent 1100 series instrument. ^{1}H, ^{13}C, ^{19}F NMR spectra were obtained on a Bruker AV-300, AVB-400, AVQ-400, or DRX-500 at room temperature. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. ^{1}H resonances are referenced to $CHCl_3$ (7.26 ppm) or DMSO-d_6 (4.90 ppm), ^{13}C resonances are referenced to $CHCl_3$ (77.23 ppm) or DMSO-d_6 (39.50 ppm), and ^{19}F resonances are referenced to $CFCl_3$ (0 ppm). Combustion analyses and high-resolution mass spectrometry analyses were performed by the University of California at Berkeley Microanalysis and Mass Spectrometry Facilities. All of the reported inhibitors displayed ≥95% purity as determined by either combustion analysis or reverse-phase HPLC using two different solvent systems.

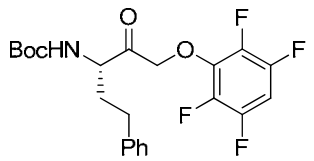
General synthesis of 2,3,5,6-tetrafluorophenoxymethyl ketone azides 2.6b-c and 2.9 (Procedure A). STEP 1: This procedure was adapted from a prior publication.[29] Isobutylchloroformate (1.1 equiv) was added to a 0.1 M solution of the azido acid[30] (1 equiv) and *N*-methyl morpholine (1.1 equiv) in THF at -40 ºC. The reaction mixture was stirred for 20 min and then cannula filtered into a flask at 0 ºC to remove the white solid. Excess diazomethane, prepared from Diazald (3.1 equiv), was introduced *in situ*, according to the literature procedure,[31] while the flask was maintained at 0 ºC. After addition of the diazomethane, the reaction flask was stoppered and was maintained at 0 ºC in a refrigerator overnight. The reaction mixture was treated with 48% aqueous HBr (3.8 equiv) and stirred for 15 min at 0 ºC. After addition of the HBr, N_2 gas evolution was observed. The reaction mixture was diluted with EtOAc (50 mL) and was then washed with 10 wt% citric acid (2 x 10 mL), saturated $NaHCO_3$ (2 x 20 mL), and saturated NaCl (1 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. STEP 2: To a 0.6 M solution of 2,3,5,6-tetrafluorophenol (3.0-3.1 equiv) in DMF at 0 ºC was added potassium fluoride (3.0 equiv), and the reaction mixture was stirred for 10 min. The appropriate bromomethyl ketone **2.5b** or **2.5c** (1.0 equiv) was then added in a small amount of DMF. The reaction mixture was stirred at 0 ºC for 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water (1x), saturated $NaHCO_3$ (1x), water (2x), and brine (1x). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by reverse-phase using 5-95% CH_3CN in H_2O with 0.1% CF_3CO_2H.



(*S*)-3-azido-1-(2,3,5,6-tetrafluorophenoxy)pentan-2-one (2.6b). Procedure A, step 1 was followed using isobutylchloroformate (0.663 mL, 5.11 mmol), 2-azidobutyric acid (0.600 g, 4.65 mmol), *N*-methyl morpholine (0.562 mL, 5.11 mmol), Diazald (3.00 g, 13.95 mmol), and 48% aqueous HBr (1.05 mL) in THF (50 mL) to afford the crude product as a pale yellow oil. Bromomethyl ketone **2.5b**, which is unstable, was taken on immediately without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, 3H, *J* = 7.4), 1.73-2.11 (m, 2H), 3.99-4.16 (m, 3H). Procedure A, step 2 was followed using bromomethyl ketone **2.5b** (0.480 g, 2.33 mmol), 2,3,5,6-tetrafluorophenol (1.16 g, 6.99 mmol), and potassium fluoride (0.406 g, 6.99 mmol) in DMF (7.0 mL) to afford 0.380 g (56%) of **2.6b** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, 3H, *J* = 7.4), 1.79-1.87 (m, 1H), 1.95-2.01 (m, 1H), 4.10 (dd, 1H, *J* = 4.9, 8.0) 5.00 (d, 1H, *J* = 17.5), 5.05 (d, 1H, *J* = 17.5), 6.78-6.85 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 10.1, 24.1, 66.9, 75.5 (t, *J* = 3.0), 99.9 (t, *J* = 23.0), 136.7-137.0 (m), 140.3 (dm, *J* = 246), 146.3 (dm, *J* = 246), 201.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.4 to -156.2 (m, 2F), -138.4 to -138.3 (m, 2F). HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{11}H_9N_3O_2F_4Li$, 298.0785; found, 298.0787.

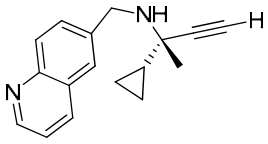


(*S*)-3-azido-1-(2,3,5,6-tetrafluorophenoxy)butan-2-one (2.6c). Procedure A, step 1 was followed using isobutylchloroformate (0.297 mL, 2.29 mmol), 2-azidopropionic acid (0.400 g, 2.08 mmol), *N*-methyl morpholine (0.251 mL, 2.29 mmol), Diazald (1.34 g, 6.24 mmol), and 48% aqueous HBr (0.47 mL) in THF (24 mL) to afford the crude product as a colorless oil. Bromomethyl ketone **2.5c**, which is unstable, was taken on immediately without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (d, 3H, *J* = 7.0), 3.91 (d, 1H, *J* = 7.0), 4.05 (d, 1H, *J* = 13.0), 4.12 (d, 1H, *J* = 13.0). Procedure A, step 2 was followed using bromomethyl ketone **2.5c** (0.17 g, 0.89 mmol), 2,3,5,6-tetrafluorophenol (0.442 g, 2.66 mmol), and potassium fluoride (0.155 g, 2.66 mmol) in DMF (2.2 mL) to afford 0.125 g (51%) of **2.6c** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J* = 7.1), 4.26 (q, 1H, *J* = 7.1) 5.03 (d, 1H, *J* = 17.7), 5.07 (d, 1H, *J* = 17.7), 6.78-6.85 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 15.3, 60.9, 75.0 (t, *J* = 3.0), 99.9 (t, *J* = 23.0), 136.8-136.9 (m), 140.3 (dm, *J* = 251), 146.3 (dm, *J* = 251), 201.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.4 to -156.3 (m, 2F), -138.5 to -138.3 (m, 2F). HRMS-FAB (m/z): $[MLi]^+$ calcd for $C_{10}H_7N_3O_2F_4Li$, 284.0629; found, 284.0631.



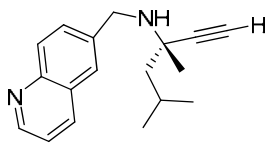
2,3,5,6-Tetrafluorophenoxymethyl ketone 2.9. Procedure A, step 1 was followed using isobutylchloroformate (0.131 mL, 1.00 mmol), Boc-L-homophenylalanine (0.250 g, 0.91 mmol), *N*-methyl morpholine (0.110 mL, 1.00 mmol), Diazald (0.585 g, 2.73 mmol), and 48% aqueous HBr (0.187 mL) in THF (9 mL) to afford the crude product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.82-1.93 (m, 1H), 2.16-2.28 (m, 1H), 2.69 (t, 2H, *J* = 7.8), 3.98 (d, 1H, *J* = 13.3), 4.04 (d, 1H, *J* = 13.3), 4.50-4.60 (m, 1H), 5.10 (d, 1H, *J* = 7.5), 7.15-7.34 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.5, 31.8, 32.2, 33.6, 57.4, 80.7, 126.7, 128.5, 128.8, 140.5, 155.5, 201.5. MS (ESI): *m/z* 356 $[MH]^+$. Procedure A, step 2 was followed using crude bromomethyl ketone **2.8**, 2,3,5,6-tetrafluorophenol (0.379 g, 2.28 mmol), and potassium fluoride (0.129 g, 2.22 mmol) in DMF (3.7 mL). Column chromatography (SiO_2, 5-25% EtOAc/hexanes) afforded 0.353 g (88%, 2 steps) of **2.9**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.80-1.92 (m, 1H), 2.19-2.29 (m, 1H), 2.71 (t, 2H, *J* = 8.0), 2.50-2.62 (m, 1H), 4.92 (d, 1H, *J* = 17.2), 4.96 (d, 1H, *J* = 17.2), 5.09 (d, 1H, *J* = 7.5), 6.72-6.85 (m, 1H), 7.15-7.34 (m, 5H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -155.8 to -156.2 (m, 2F), -138.3 to -138.5 (m, 2F).

General synthesis of quinoline propargyl amines 8b-g (Procedure B). The HCl salt of propargyl amine **7b-g**[28] (1.0-1.4 equiv) was dissolved in water and basified to pH=11 with 1 M NaOH. The aqueous layer was then extracted with toluene (3x) and the organic layers were combined, dried over Na_2SO_4, and filtered to provide a 0.25 M solution of the volatile free-based amine **7b-g** in toluene. To the solution of propargyl amine **7b-g** were added quinoline-6-carboxyaldehyde (1-1.1 equiv) and activated 4 Å molecular sieves. The reaction mixture was stirred for 16 h and then filtered through a plug of celite. The celite was washed with CH_2Cl_2 (3x). The organic washes were combined and concentrated to afford the crude imine. To a 0.2 M solution of the propargyl imine (1 equiv) in methanol at 0 ºC was added sodium borohydride (2 equiv). After stirring the reaction mixture at 0 ºC for 1 h, it was diluted with water and extracted with CH_2Cl_2 (3x). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified by silica-gel column chromatography (hexanes/ethyl acetate) to afford the pure product.

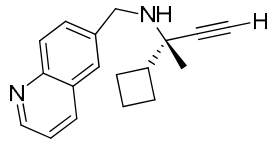


(*S*)-2-cyclopropyl-*N*-(quinolin-6-ylmethyl)but-3-yn-2-amine (2.8b). Procedure B was followed using the HCl salt of propargyl amine **2.7b** (0.105 g, 0.720 mmol) and quinoline-6-carboxyaldehyde (0.113 g, 0.720 mmol) in toluene (3.0 mL) followed by reduction with sodium borohydride (0.054 g, 1.44 mmol) in methanol (4.0 mL) to afford 0.088 g (49%) of **2.8b** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.41-0.50 (m, 3H), 0.61-0.66 (m, 1H), 0.99-1.06 (m, 1H), 1.53 (s, 3H), 2.32 (s, 1H), 4.03 (d, 1H, *J* = 12.8), 4.18 (d, 1H, *J* = 12.8), 7.39 (dd, 1H, *J* = 4.0, 8.4), 7.74 (dd, 1H, *J* = 2.0, 8.8), 7.81 (s, 1H), 8.06 (d, 1H, *J* = 8.8), 8.13 (d, 1H, *J* = 7.2),

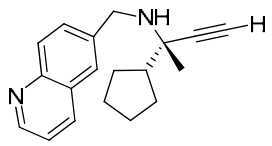
8.89 (dd, 1H, J = 1.5, 4.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 0.7, 2.6, 20.1, 28.7, 48.7, 56.2, 72.1, 84.2, 121.1, 126.3, 128.2, 129.4, 130.6, 135.8, 139.2, 147.7, 150.0.



(*S*)-3,5-dimethyl-*N*-(quinolin-6-ylmethyl)hex-1-yn-3-amine (2.8c). Procedure B was followed using the HCl salt of propargyl amine **2.7c** (0.066 g, 0.41 mmol) and quinoline-6-carboxyaldehyde (0.048 g, 0.30 mmol) in toluene (1.6 mL) followed by reduction with sodium borohydride (0.023 g, 0.60 mmol) in methanol (1.5 mL) to afford 0.053 g (66%) of **2.8c**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (d, 6H, J = 6.8), 1.41 (s, 3H), 1.50-1.67 (m, 2H), 1.93 (sept, 1H, J = 6.5), 2.40 (s, 1H), 3.99 (d, 1H, J = 12.7), 4.06 (d, 1H, J = 12.7), 7.34 (dd, 1H, J = 4.3, 8.2), 7.71 (d, 1H, J = 8.8), 7.76 (s, 1H), 8.04 (d, 1H, J = 8.7), 8.08 (d, 1H, J = 8.4), 8.80-8.89 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.7, 24.80, 24.83, 27.7, 48.3, 50.5, 53.6, 71.5, 88.6, 121.3, 126.4, 128.4, 129.6, 130.7, 136.0, 139.4, 147.8, 150.2. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{18}H_{23}N_2$, 267.1861; found, 267.1859.

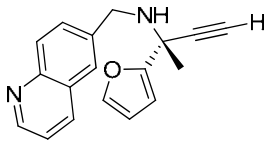


(*S*)-2-cyclobutyl-*N*-(quinolin-6-ylmethyl)but-3-yn-2-amine (2.8d). Procedure B was followed using the HCl salt of propargyl amine **2.7d** (0.111 g, 0.700 mmol) and quinoline-6-carboxyaldehyde (0.110 g, 0.700 mmol) in toluene (3.0 mL) followed by reduction with sodium borohydride (0.053 g, 1.400 mmol) in methanol (4.0 mL) to afford 0.115 g (63%) of **2.8d** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H), 1.72-1.88 (m, 2H), 1.90-1.97 (m, 2H), 2.06-2.16 (m, 2H), 2.49 (s, 1H), 2.51-2.57 (m, 1H), 3.99 (d, 1H, J = 12.7), 4.06 (d, 1H, J = 12.7), 7.38 (dd, 1H, J = 4.2, 8.3), 7.72 (dd, 1H, J = 1.8, 8.7), 7.78 (s, 1H), 8.05 (d, 1H, J = 8.6), 8.12 (d, 1H, J = 7.9), 8.87 (dd, 1H, J = 1.5, 4.2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.1, 23.9, 24.0, 24.2, 44.9, 48.6, 57.2, 72.6, 86.2, 121.1, 126.3, 128.2, 129.4, 130.6, 135.8, 139.2, 147.6, 150.0. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{18}H_{21}N_2$, 265.1699; found, 265.1706. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.50; H, 7.77; N, 10.59.

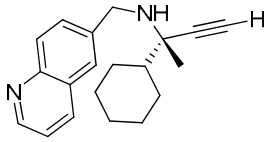


(*S*)-2-cyclopentyl-*N*-(quinolin-6-ylmethyl)but-3-yn-2-amine (2.8e). Procedure B was followed using the HCl salt of propargyl amine **2.7e** (0.050 g, 0.29 mmol) and quinoline-6-carboxyaldehyde (0.050 g, 0.32 mmol) in toluene (1.2 mL) followed by reduction with sodium borohydride (0.022 g, 0.58 mmol) in methanol (1.5 mL) to afford 0.041 g (51%) of **2.8e** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.50-1.62 (m, 4H), 1.64-1.75 (m, 2H), 1.79-1.86 (m, 2H), 2.08-2.13 (m, 1H), 2.36 (s, 1H), 3.99 (d, 1H, J = 12.8), 4.13 (d, 1H, J = 12.8),

7.38 (dd, 1H, *J* = 4.0, 8.0), 7.74 (dd, 1H, *J* = 2.0, 8.4), 7.79 (s, 1H), 8.06 (d, 1H, *J* = 8.4), 8.13 (d, 1H, *J* = 8.4), 8.88 (dd, 1H, *J* = 1.6, 4.4). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.5, 25.8, 26.0, 27.8, 28.3, 48.4, 50.2, 57.5, 71.7, 87.0, 121.2, 126.3, 128.3, 129.6, 130.7, 135.9, 139.5, 147.8, 150.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{19}H_{23}N_2$, 279.1856; found, 279.1859.



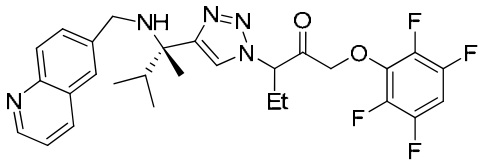
(*S*)-2-cyclohexyl-*N*-(quinolin-6-ylmethyl)but-3-yn-2-amine (2.8f). Procedure B was followed using the HCl salt of propargyl amine **2.7f** (0.290 g, 1.69 mmol) and quinoline-6-carboxyaldehyde (0.221 g, 1.41 mmol) in toluene (6.8 mL) followed by reduction with sodium borohydride (0.096 g, 2.54 mmol) in methanol (6.4 mL) to afford 0.343 g (88%) of **2.8f**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.12 (br s, 1H), 2.57 (s, 1H), 3.73 (d, 1H, *J* = 12.9), 4.08 (d, 1H, *J* = 12.9), 6.33 (dd, 1H, 3.3, 1.8), 6.47 (d, 1H, *J* = 3.0), 7.32-7.48 (m, 2H), 7.67 (dd, 1H, *J* = 1.5, 8.7), 7.74 (s, 1H), 8.03 (d, 1H, *J* = 8.7), 8.10 (d, 1H, *J* = 7.8), 8.84 (dd, 1H, *J* = 2.4, 3.0). MS (ESI): *m/z* 277 $[MH]^+$.



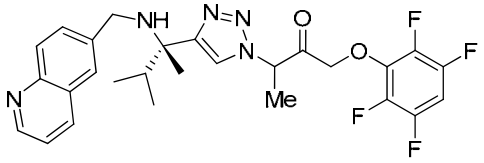
(*S*)-2-cyclohexyl-*N*-(quinolin-6-ylmethyl)but-3-yn-2-amine (2.8g). Procedure B was followed using the HCl salt of propargyl amine **2.7g** (0.145 g, 0.92 mmol) and quinoline-6-carboxyaldehyde (0.129 g, 0.69 mmol) in toluene (2.8 mL) followed by reduction with sodium borohydride (0.052 g, 1.38 mmol) in methanol (3.4 mL) to afford 0.080 g (40%) of **2.8g**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03-1.31 (m, 5H), 1.33 (s, 3H), 1.48-1.58 (m, 1H), 1.63-1.72 (m, 1H), 1.76-1.87 (m, 2H), 1.92-2.05 (m, 2H), 2.39 (s, 1H), 4.01 (d, 1H, *J* = 12.6), 4.06 (d, 1H, *J* = 12.6), 7.38 (dd, 1H, *J* = 4.1, 8.1), 7.74 (dd, 1H, *J* = 2.1, 8.7), 7.79 (s, 1H), 8.05 (d, 1H, *J* = 8.7), 8.13 (d, 1H, *J* = 8.1), 8.88 (dd, 1H, *J* = 1.7, 4.3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.8, 26.75, 26.81, 26.9, 27.0, 28.2, 46.6, 48.2, 57.1, 71.6, 88.3, 121.3, 126.4, 128.4, 129.6, 130.8, 136.0, 139.6, 147.8, 150.2. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{20}H_{25}N_2$, 293.2018; found, 293.2021.

General synthesis of 2,3,5,6-tetrafluorophenoxymethyl ketone inhibitors 2.4a-j (Procedure C). This procedure was adapted from Sharpless.[32] To a 0.25 M suspension of alkyne (1.0-1.2 equiv) and azide (1 equiv) in a 1:1 mixture of water and *tert*-butyl alcohol was added an aqueous solution of sodium ascorbate (1 equiv of a freshly prepared 1.0 M solution in water) followed by an aqueous solution copper(II) sulfate (0.1 equiv of a freshly prepared 0.3 M solution in water prepared from copper(II) sulfate pentahydrate). The heterogeneous mixture was stirred vigorously overnight. Water was added and extracted with EtOAc (3x). The organic layers were combined, washed with saturated NaCl (1x), dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by HPLC [preparatory reverse-phase C_{18} column (24.1 x 250 mm), CH_3CN/H_2O–0.1% CF_3CO_2H = 5:95 to

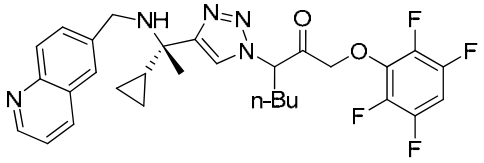
95:5 over 55 min; 10 mL/min; 254 nm detection for 65 min] and lyophilized to afford the CF_3-CO_2H salt of the product. The free amine of the product was obtained by dissolving the CF_3-CO_2H salt of the product in saturated aqueous $NaHCO_3$ and extracting with CH_2Cl_2 (4x). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.



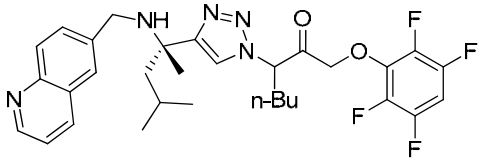
2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4a. Procedure C was followed using propargyl amine **2.8a** (0.030 g, 0.12 mmol), azide **2.6b** (0.032 g, 0.11 mmol), 1 M aqueous sodium ascorbate (0.024 g, 0.012 mmol), 0.3 M aqueous copper (II) sulfate (0.003 g, 0.012 mmol) in 1:1 *t*BuOH:H_2O (0.5 mL) to afford 33.6 mg (52%) of a 1:1 mixture of diastereomers of **2.4a** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (d, 3H, *J* = 6.6), 0.93 (t, 1.5H, J = 7.5), 0.96 (t, 1.5H, J = 7.5), 1.02 (d, 3H, *J* = 6.6), 1.50 (s, 1.5H), 1.51 (s, 1.5H), 2.03-2.21 (m, 2H), 2.33-2.37 (m, 1H), 3.59 (d, 1H, *J* = 12.9), 3.77 (d, 1H, *J* = 12.9), 4.92 (s, 2H), 5.57 (dd, 1H, *J* = 5.1, 10.2), 6.73-6.85 (m, 1H), 7.37 (dd, 1H, *J* = 4.5, 8.4), 7.57 (s, 0.5H), 7.58 (s, 0.5H), 7.67-7.69 (m, 1H), 7.73 (s, 1H), 8.02 (d, 0.5H, J = 8.7), 8.03 (d, 0.5H, J = 8.7), 8.11 (m, 1H), 8.84-8.88 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.3 to -156.2 (m, 2F), -138.0 to -137.9 (m, 2F). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{28}H_{30}N_5O_2F_4$, 544.2330; found, 544.2336. Anal. Calcd for $C_{28}H_{29}N_5O_2F_4$: C, 61.87; H, 5.38; N, 12.88. Found: C, 62.18; H, 5.40; N, 12.62.



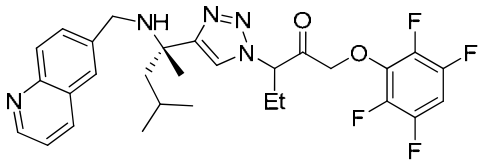
2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4b. Procedure C was followed using propargyl amine **2.8a** (0.030 g, 0.12 mmol), azide **2.6c** (0.031 g, 0.11 mmol), 1 M aqueous sodium ascorbate (0.024 g, 0.12 mmol), 0.3 M aqueous copper (II) sulfate (0.003 g, 0.012 mmol) in 1:1 *t*BuOH:H_2O (0.5 mL) to afford 27.1 mg (43%) of a 1:1 mixture of diastereomers of **2.4b** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (d, 3H, *J* = 6.9), 1.02 (d, 3H, *J* = 6.9), 1.51 (s, 3H), 1.84 (d, 1.5H, *J* = 5.1), 1.86 (d, 1.5H, *J* = 5.1), 2.17-2.22 (m, 1H), 3.61 (d, 1H, *J* = 12.9), 3.78 (d, 1H, *J* = 12.9), 4.87 (d, 1H, *J* = 16.8), 4.95 (d, 1H, *J* = 16.8), 5.74-5.80 (m, 1H), 6.73-6.84 (m, 1H), 7.37 (dd, 1H, *J* = 4.5, 8.4), 7.54 (s, 0.5H), 7.55 (s, 0.5H), 7.66- 7.73 (m, 2H), 8.02 (d, 0.5H, *J* = 8.4), 8.04 (d, 0.5H, *J* = 8.4), 8.09-8.13 (m, 1H), 8.85-8.88 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.3 to -156.2 (m, 2F), -138.0 to -137.9 (m, 2F). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{27}H_{28}N_5O_2F_4$, 530.2174; found, 530.2176. The purity of the inhibitor was determined by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in two solvent systems: CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min: 98%; CH_3OH/H_2O, 5:95 to 95:5 over 20 min, 95:5 for 10 min: 95%).



2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4c. Procedure C was followed using propargyl amine **2.8b** (0.030 g, 0.12 mmol), azide **2.6a** (0.032 g, 0.10 mmol), 1 M aqueous sodium ascorbate (0.024 g, 0.12 mmol), 0.3 M aqueous copper (II) sulfate (0.003 g, 0.012 mmol) in 1:1 *t*BuOH:H_2O (0.5 mL) to afford 33.4 mg (49%) of a 1:1 mixture of diastereomers of **2.4c** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18-0.22 (m, 1H), 0.41-0.50 (m, 3H), 0.85 (t, 1.5H, *J* = 7.0), 0.87 (t, 1.5H, *J* = 7.0), 1.15-1.22 (m, 1H), 1.25-1.40 (m, 4H), 1.54 (s, 3H), 2.02-2.08 (m, 1H), 2.20-2.33 (m, 1H), 3.74 (d, 1H, *J* = 12.6), 3.87 (d, 1H, *J* = 12.6), 4.93 (s, 2H), 5.63-5.68 (m, 1H), 6.76-6.84 (m, 1H), 7.37 (dd, 1H, *J* = 4.5, 8.4), 7.61 (s, 0.5H), 7.62 (s, 0.5H), 7.65- 7.70 (m, 1H), 7.73 (s, 1H), 8.02 (d, 0.5H, *J* = 8.4), 8.05 (d, 0.5H, *J* = 8.4), 8.09-8.13 (m, 1H), 8.84-8.88 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 to -156.1 (m, 2F), -138.0 to -137.9 (m, 2F). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{30}H_{32}N_5O_2F_4$, 570.2492; found, 570.2488. Anal. Calcd for $C_{30}H_{31}N_5O_2F_4$: C, 63.26; H, 5.49; N, 12.30. Found: C, 62.93; H, 5.50; N, 11.90.

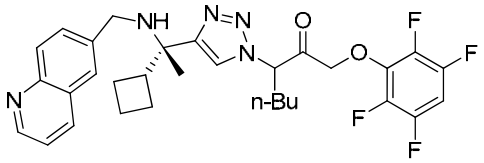


2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4d. Procedure C was followed using propargyl amine **2.8c** (0.017 g, 0.065 mmol), azide **2.6a** (0.021 g, 0.065 mmol), 1 M aqueous sodium ascorbate (0.065 mL, 0.065 mmol), 0.3 M aqueous copper(II) sulfate (0.022 mL, 0.0065 mmol) in 1:1 *t*BuOH:H_2O (0.26 mL) to afford 30.0 mg (79%) of a 1:1 mixture of diastereomers of **2.4d** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.760 (d, 1.5H, *J* = 6.6), 0.762 (d, 1.5H, *J* = 6.6), 0.83-.92 (m, 6H), 1.09-1.23 (m, 1H), 1.23-1.45 (m, 3H), 1.61 (s, 1.5H), 1.62 (s, 1.5H), 1.68-1.80 (m, 2H), 1.82-1.88 (m, 2H), 1.98-2.12 (m, 1H), 2.24-2.36 (m, 1H), 3.61 (d, 0.5H, *J* = 12.6), 3.62 (d, 0.5H, *J* = 12.6), 3.76 (d, 1H, *J* = 12.6), 4.92 (s, 2H), 5.668 (dd, 0.5H, *J* = 4.7, 10.4), 5.673 (dd, 0.5H, *J* = 4.7, 10.4), 6.75-6.85 (m, 1H), 7.38 (dd, 1H, *J* = 4.3, 8.2), 7.59 (s, 0.5H), 7.60 (s, 0.5H), 7.64-7.69 (m, 1H), 7.72 (s, 1H), 8.02 (d, 0.5H, *J* = 8.7), 8.03 (d, 0.5H, *J* = 8.7), 8.09-8.14 (m, 1H), 8.85-8.89 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 to -156.0 (m, 2F), -138.0 to -137.8 (m, 2F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{31}H_{36}N_5O_2F_4$, 586.2796; found, 586.2805. Anal. Calcd for $C_{31}H_{35}N_5O_2F_4$: C, 63.58; H, 6.02; N, 11.96. Found: C, 63.53; H, 6.18; N, 11.96.

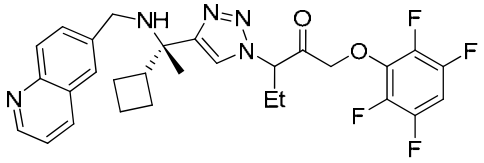


2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4e. Procedure C was followed using propargyl amine **2.8c** (0.018 g, 0.069 mmol), azide **2.6b** (0.020 g, 0.069 mmol), 1 M

aqueous sodium ascorbate (0.069 mL, 0.069 mmol), 0.3 M aqueous copper(II) sulfate (0.023 mL, 0.0069 mmol) in 1:1 *t*BuOH:H_2O (0.28 mL) to afford 26.0 mg (68%) of a 1:1 mixture of diastereomers of **2.4e** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, 3H, *J* = 6.6), 0.88-0.99 (m, 6H), 1.60 (br s, 1H), 1.61 (s, 1.5H), 1.62 (s, 1.5H), 1.70-1.80 (m, 1H), 1.82-1.88 (m, 2H), 2.04-2.15 (m, 1H), 2.30-2.42 (m, 1H), 3.62 (d, 1H, *J* = 12.7), 3.76 (d, 1H, *J* = 12.7), 4.93 (s, 2H), 5.68 (dd, 1H, *J* = 4.8, 10.3), 6.74-6.85 (m, 1H), 7.37 (dd, 1H, *J* = 4.1, 8.2), 7.59 (s, 0.5H), 7.60 (s, 0.5H), 7.64- 7.66 (m, 0.5H), 7.66-7.69 (m, 0.5H), 7.72 (s, 1H), 8.02 (d, 0.5H, *J* = 8.7), 8.03 (d, 0.5H, *J* = 8.7), 8.09-8.14 (m, 1H), 8.84-8.90 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 to -156.1 (m, 2F), -138.0 to -137.9 (m, 2F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{29}H_{32}N_5O_2F_4$, 558.2485; found, 558.2487. Anal. Calcd for $C_{29}H_{31}N_5O_2F_4$: C, 62.47; H, 5.60; N, 12.56. Found: C, 62.37; H, 5.78; N, 12.35.

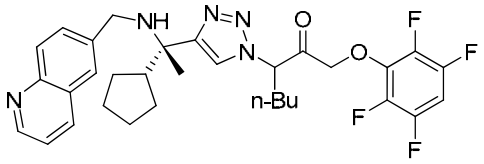


2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4f. Procedure C was followed using propargyl amine **2.8d** (0.023 g, 0.086 mmol), azide **2.6a** (0.027 g, 0.086 mmol), 1 M aqueous sodium ascorbate (0.086 mL, 0.086 mmol), 0.3 M aqueous copper(II) sulfate (0.026 mL, 0.0086 mmol) in 1:1 *t*BuOH:H_2O (0.34 mL) to afford 25.7 mg (51%) of a 1:1 mixture of diastereomers of **2.4f** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 1.5H, *J* = 7.2), 0.86 (t, 1.5H, *J* = 7.2), 1.09-1.23 (m, 1H), 1.23-1.45 (m, 4H), 1.537 (s, 1.5H), 1.542 (s, 1.5H), 1.67-2.00 (m, 7H), 2.00-2.14 (m, 1H), 2.24-2.37 (m, 1H), 2.81 (quint, 1H, *J* = 8.8), 3.63 (d, 1H, *J* = 12.8), 3.788 (d, 0.5H, *J* = 12.8), 3.794 (d, 0.5H, *J* = 12.8), 4.92 (s, 2H), 5.661 (dd, 0.5H, *J* = 4.8, 10.4), 5.665 (dd, 0.5H, *J* = 4.8, 10.4), 6.75-6.81 (m, 1H), 7.37 (dd, 1H, *J* = 4.2, 8.4), 7.58 (s, 0.5H), 7.59 (s, 0.5H), 7.686 (dd, 0.5H, *J* = 4.4, 8.8), 7.691 (dd, 0.5H, *J* = 4.4, 8.8), 7.74 (s, 1H), 8.02 (d, 0.5H, *J* = 8.8), 8.03 (d, 0.5H, *J* = 8.8), 8.09-8.14 (m, 1H), 8.84-8.89(m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 to -156.1 (m, 2F), -138.0 to -137.9 (m, 2F). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{31}H_{34}N_5O_2F_4$, 584.2643; found, 570.2649. The purity of the inhibitor was determined by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in two solvent systems: CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min: 99%; CH_3OH/H_2O, 5:95 to 95:5 over 20 min, 95:5 for 10 min: 96%).

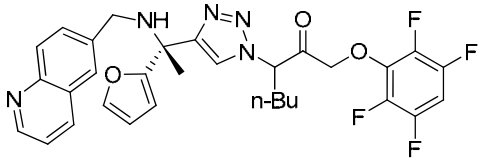


2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4g. Procedure C was followed using propargyl amine **2.8d** (0.023 g, 0.086 mmol), azide **2.6b** (0.025 g, 0.086 mmol), 1 M aqueous sodium ascorbate (0.086 mL, 0.086 mmol), 0.3 M aqueous copper(II) sulfate (0.026 mL, 0.0086 mmol) in 1:1 *t*BuOH:H_2O (0.34 mL) to afford 32.3 mg (68%) of a 1:1 mixture of diastereomers of **2.4g** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 1.5H, *J* = 7.2), 0.95 (t, 1.5H, *J* = 7.2), 1.53 (s, 1.5H), 1.54 (s, 1.5H), 1.64-1.99 (m, 7H), 2.02-2.17 (m, 1H), 2.30-2.43

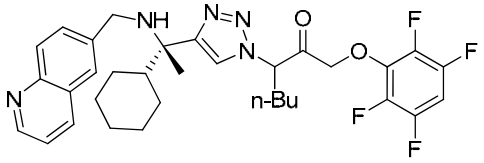
(m, 1H), 2.80 (quint, 1H, *J* = 8.8), 3.627 (d, 0.5H, *J* = 12.8), 3.631 (d, 0.5H, *J* = 12.8), 3.785 (d, 0.5H, *J* = 12.8), 3.788 (d, 0.5H, *J* = 12.8), 4.93 (s, 2H), 5.57 (dd, 0.5H, *J* = 4.8, 9.6), 5.58 (dd, 0.5H, *J* = 4.8, 9.6), 6.75-6.85 (m, 1H), 7.37 (dd, 1H, *J* = 4.4, 8.4), 7.58 (s, 0.5H), 7.59 (s, 0.5H), 7.688 (dd, 0.5H, *J* = 3.6, 8.6), 7.693 (dd, 0.5H, *J* = 3.6, 8.6), 7.74 (s, 1H), 8.02 (d, 0.5H, *J* = 8.6), 8.03 (d, 0.5H, *J* = 8.6), 8.09-8.14 (m, 1H), 8.85-8.89 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.3 to -156.1 (m, 2F), -138.0 to -137.8 (m, 2F). MS (ESI): *m/z* 556 $[MH]^+$. Anal. Calcd for $C_{29}H_{29}N_5O_2F_4$: C, 62.69; H, 5.26; N, 12.61. Found: C, 62.27; H, 5.05; N, 12.29.



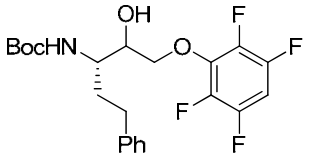
2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4h. Procedure C was followed using propargyl amine **2.8e** (0.020 g, 0.072 mmol), azide **2.6a** (0.025 g, 0.079 mmol), 1 M aqueous sodium ascorbate (0.072 mL, 0.072 mmol), 0.3 M aqueous copper(II) sulfate (0.022 mL, 0.0072 mmol) in 1:1 *t*BuOH:H_2O (0.29 mL) to afford 29.0 mg (67%) of a 1:1 mixture of diastereomers of **2.4h** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 1.5H, *J* = 7.2), 0.87 (t, 1.5H, *J* = 7.2), 1.08-1.22 (m, 1H), 1.22-1.53 (m, 9H), 1.57 (s, 1.5H), 1.58 (s, 1.5H), 1.64-1.81 (m, 3H), 1.99-2.12 (m, 1H), 2.23-2.35 (m, 1H), 2.42 (quint, 1H, *J* = 8.8), 3.64 (d, 1H, *J* = 12.8), 3.81 (d, 1H, *J* = 12.8), 4.91 (s, 2H), 5.65 (dd, 1, *J* = 4.8, 10.4), 6.76-6.84 (m, 1H), 7.38 (dd, 1H, *J* = 4.0, 8.0), 7.58 (s, 0.5H), 7.59 (s, 0.5H), 7.69 (dd, 0.5H, *J* = 4.4, 8.8), 7.70 (dd, 0.5H, *J* = 4.4, 8.8), 7.74 (s, 1H), 8.02 (d, 0.5H, *J* = 8.8), 8.03 (d, 0.5H, *J* = 8.8), 8.08-8.14 (m, 1H), 8.83-8.89 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 to -156.0 (m, 2F), -138.0 to -137.8 (m, 2F). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{32}H_{36}N_5O_2F_4$, 598.2800; found, 598.2808. Anal. Calcd for $C_{32}H_{35}N_5O_2F_4$: C, 64.31; H, 5.90; N, 11.72. Found: C, 63.99; H, 6.15; N, 11.72.



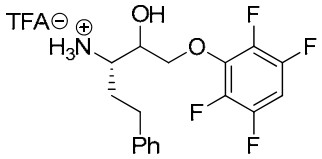
2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4i. Procedure C was followed using propargyl amine **2.8f** (0.038 g, 0.138 mmol), azide **2.6a** (0.044 g, 0.138 mmol), 1 M aqueous sodium ascorbate (0.138 mL, 0.138 mmol), 0.3 M aqueous copper(II) sulfate (0.046 mL, 0.014 mmol) in 1:1 *t*BuOH:H_2O (0.55 mL) to afford 40.0 mg (49%) of of **2.4i**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J* = 7.2), 1.12-1.46 (m, 4H), 1.72 (br s, 1H), 1.92-2.12 (m, 1H), 1.96 (s, 3H), 2.21-2.33 (m, 1H), 3.75 (d, 1H, *J* = 12.9), 3.83 (d, 1H, *J* = 12.9), 4.91 (s, 2H), 5.64 (d, 1H, *J* = 5.1, 9.9), 6.36 (s, 2H), 6.73-6.85 (m, 1H), 7.37 (dd, 1H, *J* = 4.2, 8.4), 7.42 (s, 1H), 7.63-7.68 (m, 2H), 7.75 (s, 1H), 8.03 (d, 1H, *J* = 8.4), 8.11 (d, 1H, *J* = 8.1), 8.83-8.91 (m, 1H). MS (ESI): *m/z* 596 $[MH]^+$. The purity of the inhibitor was determined by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min: 99%).



2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.4j. Procedure C was followed using propargyl amine **2.8g** (0.024 g, 0.082 mmol), azide **2.6a** (0.026 g, 0.082 mmol), 1 M aqueous sodium ascorbate (0.082 mL, 0.082 mmol), 0.3 M aqueous copper(II) sulfate (0.027 mL, 0.0082 mmol) in 1:1 *t*BuOH:H_2O (0.33 mL) to afford 33.5 mg (67%) of a 1:1 mixture of diastereomers of **2.4j** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 1.5H, *J* = 7.2), 0.87 (t, 1.5H, *J* = 7.2), 0.91-1.11 (m, 2H), 1.12-1.43 (m, 6H), 1.51 (s, 1.5H), 1.52 (s, 1.5H), 1.56-1.73 (m, 5H), 1.74-1.86 (m, 2H), 2.01-2.12 (m, 2H), 2.24-2.37 (m, 1H), 3.58 (d, 1H, *J* = 13.0), 3.77 (d, 1H, *J* = 13.0), 4.92 (s, 2H), 5.62-5.69 (m, 1H), 6.75-6.85 (m, 1H), 7.37 (dd, 1H, *J* = 4.2, 8.3), 7.55 (s, 0.5H), 7.56 (s, 0.5H), 7.65- 7.70 (m, 1H), 7.72 (s, 1H), 8.01 (d, 0.5H, *J* = 8.8), 8.02 (d, 0.5H, *J* = 8.8), 8.09-8.14 (m, 1H), 8.85-8.89 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ -156.2 to -156.1 (m, 2F), -138.0 to -137.9 (m, 2F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{33}H_{38}N_5O_2F_4$, 612.2971; found, 612.2962. Anal. Calcd for $C_{33}H_{37}N_5O_2F_4$: C, 64.80; H, 6.10; N, 11.45. Found: C, 64.51; H, 6.46; N, 11.14.

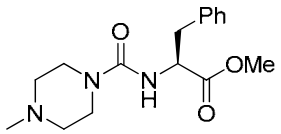


2,3,5,6-Tetrafluorophenoxymethyl alcohol 2.10. To a 0.06 M solution of ketone **2.9** (0.280 g, 0.64 mmol) in 1:1 MeOH/THF (9.9 mL) at 0 ºC, was added sodium borohydride (0.097 g, 2.57 mmol). After stirring at 0 ºC for 4 h, the mixture was concentrated and then diluted with 1:1 EtOAc/saturated aqueous NH_4Cl (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 10-40% EtOAc/hexanes) afforded 0.265 g (95% yield) of **2.10** as a sticky white solid. ^{1}H NMR (400 MHz, MeOD-*d*$_4$): δ δ 1.45 (s, 9H), 1.63-1.75 (m, 1H), 1.99-2.11 (m, 1H), 2.51-2.64 (m, 1H), 2.66-2.80 (m, 1H), 3.52-3.63 (m, 1H), 3.75-3.81 (m, 1H), 413-4.22 (m, 1H), 4.29 (dd, 1H, *J* = 3.6, 10.4), 4.62 (br s, 1H), 6.62-6.78 (m, 1H), 7.03-7.29 (m, 5H). MS (ESI): *m/z* 466 $[MNa]^+$.

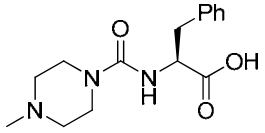


2,3,5,6-Tetrafluorophenoxymethyl alcohol 2.6. A solution of 95:2.5:2.5 CF_3CO_2H /H_2O/iPr_3SiH (1.2 mL/0.03 mL/0.03 mL) was added to alcohol **2.10**. After stirring for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to afford 267 mg (99%) of the amine trifluoroacetate salt **2.6**. ^{1}H NMR (300 MHz, MeOD-*d*$_4$): δ 1.91-1.12 (m,

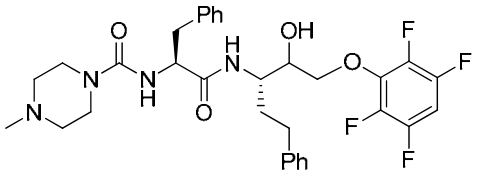
2H), 2.65-2.91 (m, 2H), 3.42-3.53 (m, 1H), 4.19-4.30 (m, 2H), 4.32-4.40 (m, 1H), 7.09-7.31 (m, 6H). MS (ESI): *m/z* 344 $[MH]^+$.



Methyl ester 2.12. A 0.05 M solution of homophenylalanine·HCl (1.00 g, 4.64 mmol) in 1:1 CH_2Cl_2/saturated aqueous $NaHCO_3$ (93 mL) was cooled to 0 ºC and stirred vigorously for 10 min. Phosgene was then added as a 20% solution in toluene (4.90 mL, 9.27 mmol), and the reaction mixture was stirred for an additional 10 min. The organic and aqueous layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford isocyanate **2.11** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (dd, 1H, *J* = 6.5, 13.3), 3.18 (dd, 1H, *J* = 5.1, 13.3), 3.81 (s, 3H), 4.21-4.32 (m, 1H), 7.10-7.40 (m, 5H). MS (ESI): *m/z* 206 $[MH]^+$. To a 0.2 M solution of crude isocyanate **2.12** in CH_2Cl_2 was added *N*-methylpiperazine (1.03 mL, 9.27 mmol). The reaction mixture was stirred for 20 h and concentrated under reduced pressure. Crystallization from EtOAc/hexanes afforded 0.78 g (55%) of **2.x** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.34-2.40 (m, 4H), 3.06-3.20 (m, 2H), 3.29-3.44 (m, 4H), 3.74 (s, 3H), 4.79 (dt, 1H, *J* = 5.9, 13.0), 4.88 (d, 1H, *J* = 7.8), 7.08-7.13 (m, 2H), 7.22-7.32 (m, 3H).^{13}C-NMR (100 MHz, $CDCl_3$): δ 38.5, 43.8, 46.2, 52.4, 54.5, 54.7, 127.2, 128.7, 129.5, 136.4, 156.6, 173.3. MS (ESI): *m/z* 306 $[MH]^+$.

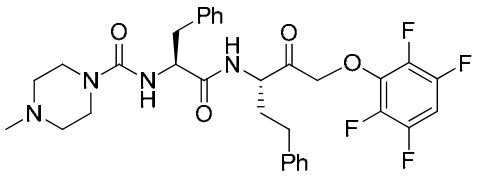


Carboxylic acid 2.7. To a 0.27 M solution of ester **2.7** (0.77 g, 2.5 mmol) in degassed dioxane (9.3 mL), was added a 0.25 M solution of $LiOH·H_2O$ (0.21 g, 5.0 mmol) in degassed H_2O (10 mL). The reaction mixture was stirred overnight. The dioxane was then removed by concentrating under reduced pressure and the water was removed by lyophilization to afford crude **2.x**. Carboxylic acid **2.x** was taken on without purification. ^{1}H NMR (400 MHz, MeOD-*d*$_4$): δ 2.28 (s, 3H), 2.30-2.41 (m, 4H), 3.01 (dd, 1H, *J* = 6.5, 13.3), 3.18 (dd, 1H, *J* = 5.1, 13.3), 3.25-3.43 (m, 4H), 4.42 (app t, 1H, *J* = 5.8), 7.11-7.25 (m, 5H). ^{13}C-NMR (100 MHz, MeOD-*d*$_4$): δ 39.8, 44.5, 46.2, 55.7, 58.4, 127.3, 129.2, 130.9, 139.9, 159.0, 179.0. MS (ESI): *m/z* 292 $[MH]^+$.



2,3,5,6-Tetrafluorophenoxymethyl alcohol 2.13. To a 0.3 M solution of carboxylic acid **2.7** (0.048 g, 0.16 mmol) in DMF (0.7 mL) cooled to 0 ºC, was added *N*-methylmorpholine

(0.071 mL, 0.66 mmol) followed by HOAt (0.029 g, 0.21 mmol). Amine **2.6** (0.15 g, 0.33 mmol) was then added and then EDC (0.041 mg, 0.21 mmol) was added last. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was diluted EtOAc (10 mL) and washed with water (5 mL), 5% aq. $KHSO_4$ (5 mL), and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford alcohol **2.13**, which was taken on without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57-1.83 (m, 2H), 2.28 (s, 3H), 2.20-2.46 (m, 6H), 3.02-3.12 (m, 2H), 3.22-3.39 (m, 4H), 3.89-4.00 (m, 1H), 4.02-4.26 (m, 3H), 4.30-4.45 (m, 1H), 4.96 (d, 1H, J = 6.6), 6.33 (d, 1H, J = 9.0), 6.72-6.86 (m, 1H), 7.06-7.16 (m, 2H), 7.17-7.36 (m, 8H). MS (ESI): *m/z* 617 $[MH]^+$.



2,3,5,6-Tetrafluorophenoxymethyl ketone inhibitor 2.5. Dess-Martin periodinane (0.107 g, 0.252 mmol) was added to a 0.28 M solution of crude alcohol **2.13** (0.052 g, 0.084 mmol) in water-saturated CH_2Cl_2 (0.3 mL). The reaction mixture was stirred for 2 h and then diluted with diethyl ether (5 mL), and a solution of sodium thiosulfate (0.292 g, 0.924 mmol) in 80% saturated aqueous $NaHCO_3$ (0.3 mL). The mixture was stirred rapidly for 45 min. The layers were separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ (10 mL), water (2 x 10 mL), and saturated NaCl (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by reverse phase purification (Biotage C18SH column, 5-95% CH_3CN/H_2O + 0.1% CF_3CO_2H). The fractions containing product were combined and the acetonitrile was removed by concentrating under reduced pressure. The remaining aqueous solvent was basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 8.4 mg (16%) of **2.5**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71-1.87 (m, 1H), 2.06-2.20 (m, 1H), 2.28 (s, 3H), 2.29-2.37 (m, 4H), 2.47 (app t, 2H, J = 7.8), 3.02-3.13 (m, 2H), 3.25-3.40 (m, 4H), 4.56 (dd, 1H, J = 7.2, 14.7), 4.62-4.71 (m, 1H), 4.85-4.97 (m, 3H), 6.68-6.85 (m, 2H), 7.06-7.14 (m, 2H), 7.16-7.35 (m, 8H). MS (ESI): *m/z* 615 $[MH]^+$. The purity of the inhibitor was determined by HPLC-MS analysis (C18 column (2.1 x 150 mm); 0.4 mL/min; 254 nm detection in CH_3CN/H_2O-0.1% CF_3CO_2H, 5:95 to 95:5 over 16 min, 95:5 for 2 min: 95%).

Cruzain inhibition assay. The k_{inact}/K_i for inhibitors were determined under pseudo-first order conditions using the progress curve method.[33] The proteolytic cleavage of *N*-acyl aminocoumarins by cruzain was conducted in Dynatech Microfluor fluorescence 96-well microtiter plates. Assay wells contained a mixture of inhibitor and 1.0 μM of Cbz-Phe-Arg-AMC (K_m = 1.1 μM; purchased from Bachem) in buffer (100 mM solution of pH 6.3 sodium phosphate buffer with 400 mM of sodium chloride, 5 mM of DTT, 10 mM of EDTA, and 0.025% Triton-X 100). Aliquots of cruzain were added to each well to initiate the assay. The final enzyme concentration was 0.1 nM. Hydrolysis of the AMC substrate was monitored fluorometrically for 25 min using a Molecular Devices Spectra Max Gemini SX instrument. The

excitation wavelength was 350 nm and the emission wavelength was 450 nm, with a cutoff of 435 nm. To determine the inhibition parameters, time points for which the control ([I] = 0) was linear were used. For each inhibitor, a k_{obs} was calculated for at least four different concentrations of inhibitors via a nonlinear regression of the data according to the equation $P = (v_i/k_{obs})[1-\exp(-k_{obs}t)$ (where product formation = P, initial rate = v_i, time = t, and the first-order rate constant = k_{obs}) using Prism 5 (GraphPad). For all inhibitors k_{obs} varied hyperbolically with [I] and non-linear regression analysis was performed with Prism to determine k_{inact}/K_i using $k_{obs} = k_{inact}[I]/([I]+K_{i*}(1+[S]/K_m))$. Inhibition was measured at least in triplicate and the average and standard deviation of the assays is reported.

***T. cruzi* cell culture assay.** Mammalian cells were cultured in RPMI-1640 medium supplemented with 5% heat-inactivated fetal calf serum (FCS) at 37 °C in 5% CO_2. The Y strain of *T. cruzi* was maintained by serial passage in bovine embryo skeletal muscle (BESM) cells. Infectious trypomastigotes were collected from culture supernatants. A BESM cell suspension was dispensed into sterile 96 well black plates with clear bottom (Greiner Bio-One). Following cell attachment, cultures were infected with *T. cruzi* trypomastigotes. After infection, the culture medium was removed and replaced with 200 µL of fresh culture medium containing several concentrations of the test inhibitors (0, 0.3, 1, 3, and 10 µM). Culture plates were incubated for 72 h, washed once with PBS and fixed for 2 hours with 4 % paraformaldehyde. Following a PBS wash to remove the fixative, host cell and parasite DNAs were labeled with 0.1 µg/mL DAPI. Plates were kept in the dark at 4 ^oC until used for image acquisition by the IN Cell Analyzer 1000 imager (GE Healthcare) with a 10x objective. Ten image fields comprising 200-300 host cells were acquired per well. The IN Cell Workstation 3.5 Multi Target Analysis Module was used for image analysis. Image segmentation parameters were set to identify host nuclei segmented with a minimum area of 150 μm^2, and intracellular parasite nuclei with an area size of 2-4 μm^2. Parasite nuclei/ host nuclei ratios were selected as measurement output and the average of duplicate or triplicate runs were used to generate IC_{50} plots.

Cloning and generation of the cruzain *N*-glycosylation mutant construct. A construct containing the cruzain gene cloned into the yeast expression vector pPICZα C was kindly provided by Rafaela Ferreira (UCSF). Site-directed mutagenesis with the QuickChange™ system (Stratagene) was carried out to incorporate point mutations at two glycosylation sites, Ser49Ala and Ser172Gly (mature domain numbering). The mutated sites were introduced into the construct using the following primers: GCCACCCGCTGACGAACCTG**GCG**GAGCAGATGCTCGTGTCG (site 1, forward), CGGTGGGCGACTGCTTGGAC**CGC**CTCGTCTACGAGCACAGC (site 1, reverse), CTTCTCGTCGGCTACAATGAC**GGC**GCCGCAGTGCCGTACTGG (site 2, forward),GAAGAGCAGCCGATGTTACTG**CCG**CGGCGTCACGGCATGACC (site 2, reverse). Incorporation of the mutations and confirmation of an intact cruzain-S49A_S172G construct were confirmed by DNA sequencing performed at Elim Biopharmaceuticals Inc. (Hayward, CA).

Expression, purification and inhibition of cruzain-S49A_S172G. *Pichia pastoris* strain X33 was transformed with the cruzain-S49A_S172G construct by electroporation. A 10ml starter culture of YPD media containing 100µg/ml zeocin was inoculated with a single, transformed colony and the culture was grown overnight at 30°C. Four liters of YPD-zeocin

media was inoculated with the starter culture and incubated at 30°C, with constant shaking, for three days. Cells were harvested by centrifugation at 2500rpm for 15mins and the pellet was dissolved in 1200ml of BMM media. Induction of protein overexpression was carried out in a BioFlo110 Fermentor/Bioreactor (New Brunswick Scientific), with the addition of 1% methanol twice a day. The culture was maintained at pH 4.5 for autocatalytic activation of the cruzain zymogen to produce the mature, active form during cell culture. The supernatant was collected after 3 days, concentrated to 75ml using an Ultrasette™ screen channel tangential flow device (Pall Corporation) with a 10kDa cut-off and adjusted to pH 7.0 with NaOH. The sample was then adjusted with final concentrations of 300mM NaCl and 10mM imidazole and incubated at 4°C with 5ml of Ni-NTA beads on an orbital shaker. After 2 hours the mixture was applied to an empty PD-10 column (GE Healthcare). The column was washed with a buffer consisting of 300mM NaCl, 10mM imidazole and 100mM potassium phosphate pH 6 and proteins were eluted with a buffer consisting of 200mM imidazole, 300mM NaCl and 100mm potassium phosphate pH 6. The activity of mature, purified cruzain was measured with Z-FR-AMC and completely abolished with molar excess amounts of **2**. The inhibited sample was dialyzed against 20mM Bis-Tris pH5.8 and applied to a Mono-Q anion exchange column (GE Healthcare). Fractions corresponding to mature cruzain on SDS-PAGE (approximately 27kDa) were pooled, dialyzed against 2mM Bis-Tris pH 5.8 and concentrated to 8mg/ml for crystallization.

Crystallization and data collection. Cruzain was recombinantly expressed and purified (see Supporting Information for experimental details). Crystallization conditions were screened with the Mosquito® drop-setting system (TTP Labtech) against a number of commercially available kits. Conditions yielding crystals (20 % PEG 3000, 0.1 M Sodium acetate pH 4.5) were reproduced in a 24-well format using 500 μl of crystallization solution per well and hanging drops consisting of 1 μl of protein and 1 μl of well solution. Crystals were flash-cooled in well solution supplemented with 30% ethylene glycol and mounted in a cassette for the Stanford Auto Mounter (SAM) system.[34] Diffraction data were collected at the Stanford Synchrotron Radiation Lightsource (SSRL). Cruzain•**2** data were collected to 1.20Å on BL7-1 at a temperature of 100K and λ=0.98Å after selecting an optimal crystal from screening performed with the robotic SAM system. Reflections were indexed and integrated in the primitive monoclinic setting using MOSFLM[35] and scaled and merged in spacegroup $P2_1$ with SCALA[36]. Intensities were then converted to structure factor amplitudes in TRUNCATE.[37] The cruzain•**2** structure was solved by molecular replacement in MOLREP[38] using a high resolution structure of cruzain bound to a hydroxymethyl ketone inhibitor (PDB ID 1ME3). A single, clear rotation function solution was obtained at greater than 3 x peak height/σ of the second highest solution, suggesting one molecule of cruzain in the asymmetric unit. The translation function yielded a clear solution for the monomer with a score of 0.67 and initial R_{work} of 34.6%. Rigid body refinement, followed by simulated annealing and grouped B-factor refinement in CNS[39] gave an R_{free} of 28.56% an R_{work} of 26.88% and yielded electron density maps of excellent quality. The inhibitor molecule was placed into mFo-DFc difference electron density contoured at the 3σ level using COOT.[40] The resulting coordinates were refined through a combination of simulated annealing, positional and isotropic B-factor refinement in CNS. The model was completed by interspersing rounds of positional and anisotropic B-factor refinement in REFMAC5[41] with manual adjustments in COOT. The structure has excellent stereochemistry, as determined by MOLPROBITY[42], with 96.6% of residues in the favored regions, 100% in allowed regions and no outliers. The final model contains 1 molecule of mature cruzain, 1 molecule of **2**, 265 water molecules and 4

molecules of ethylene glycol. Statistics for data collection and refinement are given in Table 2.3**.** The coordinates and observed structure factors amplitudes for each model have been deposited in the Protein Data Bank under accession code 3IUT.

Table 2.3. X-ray data collection and refinement statistics

	cruzain•**2.2**
Data collection	
Space group	$P2_1$
Cell dimensions	1.20 (1.26-1.20)
a, *b*, *c* (Å)	44.08, 51.45, 45.85
α, β, γ (°)	90.0, 115.5, 90.0
Resolution (Å)	1.20 (1.26-1.20)[a]
R_{merge}	0.062 (0.34)
$I / \sigma I$	19.1 (6.2)
Completeness (%)	97.9 (88.7)
Redundancy	6.4 (5.7)
Refinement	
Resolution (Å)	38.0-1.20
No. reflections	53757
R_{work} / R_{free}	0.12/0.15
No. atoms	
Protein	1664
Ligand/ion	46
Water	265
B-factors	
Protein	9.82
Inhibitor	11.65
Ethylene glycol	18.63
R.m.s. deviations	
Bond lengths (Å)	0.019
Bond angles (°)	1.91

[a] A single crystal was used for data collection.

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Chapter 3. Asymmetric Rhodium(I)-Catalyzed Addition of Alkenyl Trifluoroborates and MIDA Boronates to Activated Aldimines.

The rhodium(I)-catalyzed addition of alkenylboron reagents to imines is described. The diastereoselective addition of alkenyl trifluoroborates to both aromatic and aliphatic N-tert-butanesulfinyl aldimines provides α-branched allylic amines in good yields and with very high selectivity. The method is also extended to the addition of MIDA boronates to N-tert-butanesulfinyl aromatic imines, which in comparison to trifluoroborates proceed with higher yields and diastereoselectivities. The chemistry is demonstrated to be compatible with a variety of electronically and sterically diverse N-sulfinyl imines and alkenyl boron reagents. This new methodology enables the general and efficient asymmetric synthesis of the important class of α-branched allylic amines from readily available and stable starting materials. The *majority of this work has been published in communications* (Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850-3851 and Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, submitted).

The enantioselective addition of alkenylboron reagents to activated imines is also explored, in brief. A cationic rhodium complex and a phosphoramidite ligand are found to catalyze the addition of cinnamyl trifluoroborate to N-Boc and N-tosyl benzaldimine in moderate yield and enantioselectivity. These preliminary results support further exploration of the scope of this transformation for the development of a general, enantioselective rhodium-catalyzed addition of alkenylboron reagents to imines.

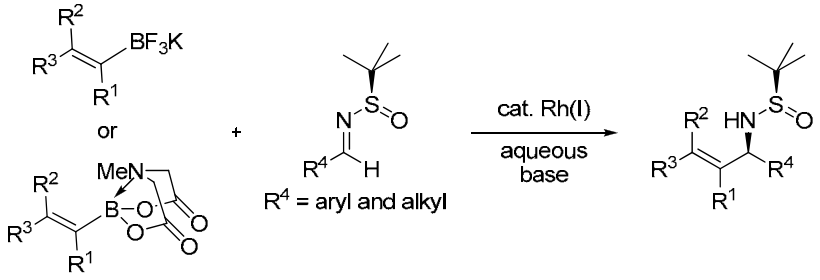
Authorship

The work on the alkenylation of *N*-*tert*-butanesulfinyl imino ethers was conducted in collaboration with Kimberly Barrett, an undergraduate who I mentored.

Introduction

The development of efficient and practical methods for the asymmetric synthesis of chiral, α-branched amines is of great importance due to the ubiquitous nature of this motif in pharmaceutical agents and natural products.[1] The Rh(I)-catalyzed addition of arylboron reagents to activated imines has emerged as a general, functional-group tolerant method for the asymmetric synthesis of α-aryl branched amines.[2,3] In contrast, despite the clear synthetic importance of α-branched allylic amines,[4,5] the corresponding Rh(I)-catalyzed addition of alkenylboron reagents to imines had yet to be reported at the time we initiated this research.[6,7] In this chapter, we describe the development of a practical and highly stereoselective Rh(I)-catalyzed addition of alkenyl trifluoroborates and MIDA boronates to *N*-*tert*-butanesulfinyl imines (Scheme 3.1).

Scheme 3.1. Addition of alkenyl trifluoroborates and MIDA boronates to *N*-sulfinyl imines



A key challenge for the rhodium-catalyzed addition of boronic acids to electrophiles such as imines is competitive decomposition of the boron reagent. The same conditions, namely heat, water, and transition-metal catalysts that promote the addition of boron reagents also accelerate their decomposition via pathways such as protodeboronation, oxidation, and/or polymerization.[8] Therefore, overcoming these undesired processes has posed a particular challenge. While using a large excess[9] or slow addition[3d] of the boronic acid has resulted in improved yields, these approaches are wasteful and impractical.

Although boronic acids are highly versatile coupling reagents,[10] their limited stability and incompatibility with many synthetic reagents have resulted in the development of several important surrogates. Potassium trifluoroborates,[11] and even more recently, *N*-methyliminodiacetic acid (MIDA) boronates,[12] have emerged as particularly attractive alternative organoboron coupling partners.[13,14] These boron reagents exhibit exceptional bench-top stability, are easy to synthesize and isolate, and are compatible with many synthetic reagents. Furthermore, MIDA boronates are stable to silica gel chromatography, allowing for expanded utility in the synthesis of complex organoboron building blocks.[15]

MIDA boronates are inert to many of the common pathways of decomposition; however, they are also unreactive toward transmetallation.[16] Burke and coworkers have elegantly demonstrated that cross-coupling of unstable boronic acids, via the in situ, rate-controlled

hydrolysis of MIDA boronates, is a general solution for the Suzuki-Miyaura reaction.[17] The slow-release of boronic acids from MIDA boronates maintains minimal amounts of free boronic acid throughout the reaction, which results in improved efficiency. Taking advantage of the hydrolytic stability of *N*-*tert*-butanesulfinyl aromatic imines, we report herein the application of MIDA boronates in the Rh(I)-catalyzed addition to imines. By using MIDA boronates as the addition reagents, decomposition of the boron reagent is minimized and higher yields are attained for most substrate classes. The substrate scope for the Rh(I)-catalyzed alkenylation is explored and a comparison of the trifluoroborate and MIDA boronate efficiencies is provided.

Diastereoselective Addition of Alkenyl Boron Reagents to *N*-Sulfinyl Aldimines

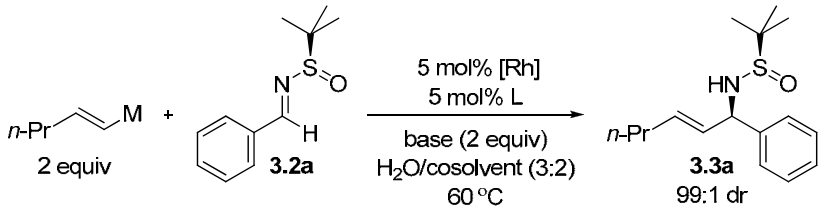
Optimization Studies for the Addition of Alkenyl Trifluoroborates to N-Sulfinyl Imines

With the goal of developing a general and efficient method for the synthesis of α-branched allylic amines from readily available and stable starting materials, we began by evaluating the reaction between *N*-*tert*-butanesulfinyl imines and potassium alkenyl trifluoroborates. *N*-Sulfinyl imines are appealing due to their ease of synthesis and hydrolytic stability even at elevated temperatures. The facile deprotection of the sulfinyl group after amine synthesis is an important additional desirable attribute.[18] Trifluoroborates are attractive boron coupling partners as they are easily prepared from boronic acids by reacting with the inexpensive reagent KHF_2 and are isolated as monomeric crystalline salts by recrystallization.[19,20] They are more stable towards air and moisture and generally exhibit greater reactivity in transition-metal catalyzed processes than their boronic acid counterparts.[11]

In the Rh(I)-catalyzed reaction of sulfinyl imine **3.2a** and pentenyltrifluoroborate **3.1a**, a small amount of product was first observed using aqueous basic conditions and a cationic rhodium catalyst (Table 3.1, entry 1). The addition of the phosphine ligand was subsequently found to result in a large increase in yield (entry 2). Many phosphine ligands were screened, however, 1,2-bis(diphenylphosphino)benzene (dppbenz) formed the most active catalyst system by a large margin.[21] A solvent screen established a correlation between the efficiency of the reaction and the solubility profile of trifluoroborates.[11] Polar cosolvents in which trifluoroborates show high solubility such as methanol, acetone, and dimethylformamide (DMF) resulted in higher yields than nonpolar cosolvents such as toluene and 1,2-dichloroethane in which trifluoroborates are poorly soluble. DMF was found to be the optimal cosolvent (entry 3).

Upon evaluating commercially available and air-stable precatalysts, $Rh[(cod)(Cl)]_2$ and $Rh[(OH)(cod)]_2$ were found to be highly effective as well (Table 3.1, entries 4-5). $Rh[(cod)(OH)]_2$ was the most active precatalyst, which is consistent with the reaction proceeding via a Rh-OH species. Notably, catalyst loadings as low as 1 mol% $[Rh(cod)(OH)]_2$ can be employed without reduction in yield (entry 6). A base screen established that while NEt_3 was optimal, K_3PO_4 and Cs_2CO_3 also resulted in high conversions (entries 7-9). It was also confirmed that trifluoroborate salts are much more effective than boronic acids in the Rh-catalyzed alkenylation (entry 10). Remarkably, the diastereoselectivity was excellent (99:1) regardless of the conditions.

Table 3.1. Optimization of reaction conditions for the addition of alkenyl trifluoroborates

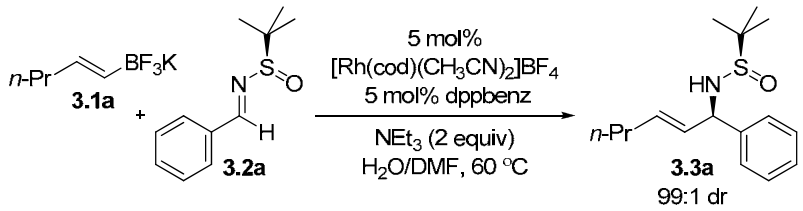


entry	catalyst and ligand	M	base	co-solvent	yield (%)[a]
1	$[Rh(cod)(CH_3CN)_2]BF_4$	BF_3K	NEt_3	dioxane	5
2	$[Rh(cod)(CH_3CN)_2]BF_4$, dppbenz	BF_3K	NEt_3	dioxane	61
3	$[Rh(cod)(CH_3CN)_2]BF_4$, dppbenz	BF_3K	NEt_3	DMF	73
4	$[Rh(cod)(Cl)]_2$, dppbenz	BF_3K	NEt_3	DMF	70
5	$[Rh(cod)(OH)]_2$, dppbenz	BF_3K	NEt_3	DMF	82
6[b]	$[Rh(cod)(OH)]_2$, dppbenz	BF_3K	NEt_3	DMF	81
7[c]	$[Rh(cod)(OH)]_2$, dppbenz	BF_3K	K_3PO_4	DMF	84
8	$[Rh(cod)(OH)]_2$, dppbenz	BF_3K	Cs_2CO_3	DMF	68
9	$[Rh(cod)(OH)]_2$, dppbenz	BF_3K	CsF	DMF	44
10	$[Rh(cod)(OH)]_2$, dppbenz	$B(OH)_2$	NEt_3	DMF	40

[a] Yields were determined by ^1H NMR relative to an external standard. [b] Reaction was run with 1 mol% $[Rh(cod)(OH)]_2$ and 2 mol% dppbenz. [c] For aliphatic imines the yields were ~20% lower with K_3PO_4.

The best results were obtained with a solvent system consisting of at least 60% water (Table 3.2, entry 1). It is worth noting that at room temperature several of the reagents are insoluble. Upon heating and stirring, the reaction mixture becomes biphasic with globules of starting imine/product in the reaction medium. The trifluoroborate, on the other hand, remains dissolved in the water/DMF solvent system. Interestingly, decreasing the amount of water to 40% results in a homogenous reaction but a lower yield (entry 2). In contrast, the amount of water could be increased up to 80% while maintaining a high yield (entry 3). However, the reaction cannot be performed in pure water due to the insolubility of the imine starting material (entry 4). Because a biphasic mixture is essential for achieving high conversion, the reaction might proceed on the surface of the aqueous reaction medium. Rate acceleration for reactions occurring in water has been attributed to effects such as hydrophobic aggregation, increased cohesive energy density, and ground-state destabilization.[22] For reactions occurring on water, hydrogen bond interactions of the water surface with the reactants and, even more importantly, transition state could be responsible for the observed rate enhancements.[23] Importantly, the reaction does not show scale dependence despite its biphasic nature. Furthermore, on large scale the biphasic reaction system allows for the isolation of product via a simple separation of the product phase.

Table 3.2. Reaction yield with various amounts of water



entry	solvent system	yield (%)[a]
1	60% H_2O in DMF	77
2	40% H_2O in DMF	33
3	80% H_2O in DMF	78
4	100% H_2O[b]	3

[a] Yields were determined by ^1H NMR relative to an external standard. [b] The trifluoroborate and rhodium catalyst are insoluble in this solvent system.

Scope in N-Sulfinyl Aromatic Aldimine for the Addition of Alkenyl Trifluoroborates

Having identified optimal conditions for the addition of trifluoroborates, we began by investigating the scope of the methodology with the alkenylation of various *N-tert*-butanesulfinyl aromatic aldimines with pentenyltrifluoroborate **3.1a** (Table 3.3). Electron-neutral (entries 1-4) and electron-deficient (entries 5-8) *N*-sulfinyl imines provided the corresponding allylic amines in excellent yields with high diastereoselectivity. Addition to *N*-sulfinyl ortho-methylbenzaldimine and ortho-chlorobenzaldimine demonstrates the steric tolerance of the method (entries 4-5). Furthermore, the alkenylation of *N*-sulfinyl 3-acetylbenzaldimine in high yield serves to highlight the functional group compatibility of the method (entry 8).[24]

The addition to electron-rich *N*-sulfinyl 4-methoxyphenyl and 2-furanyl imines proceeded with high selectivity, although only in moderate yield (entries 9-10). After careful evaluation of the reaction conditions, it was found that the alkenylation reaction ceases after 1 h even though significant quantities of the hydrolytically stable aryl *N-tert*-butanesulfinyl imines are still present (eq 3.1). Interestingly, the addition of another two equivalents of the trifluoroborate after 1 h resulted in higher yields. This suggested that over a period of 1 h, the Rh(I)-catalyst remains active while significant consumption of the trifluoroborate has occurred through a combination of addition and decomposition.

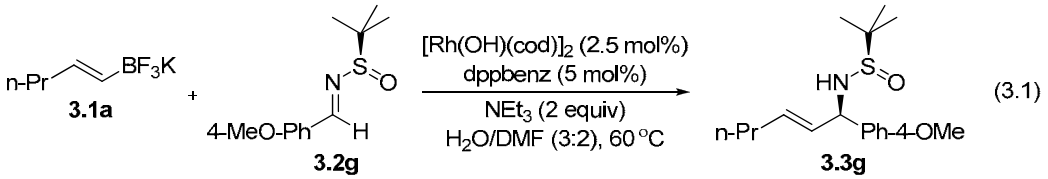
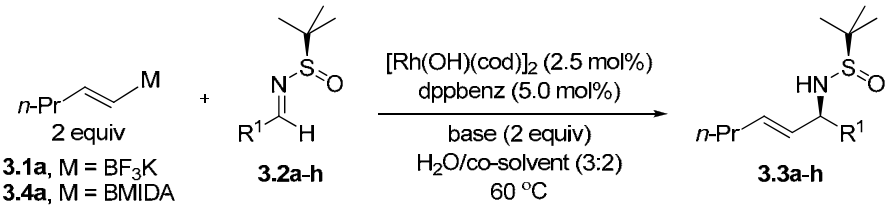
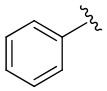
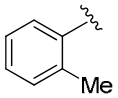
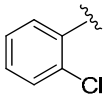
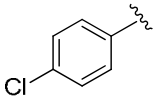
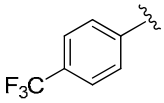
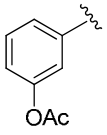
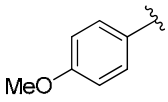
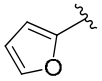


Table 3.3. Scope in *N-tert*-butanesulfinyl aromatic imine with trifluoroborates and MIDA boronates

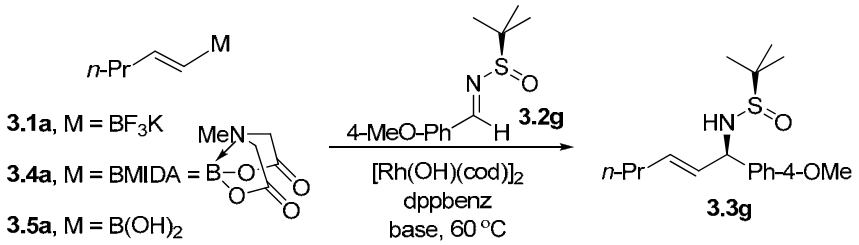


entry	imine **3.2**	**3.3**	M = BF_3K[a] isolated yield (%)	BMIDA[b] isolated yield (%)	dr[c]
1		**3.2a** **3.3a**	82	98	99:1
2[d]			82	92	99:1
3[e]			75	96	99:1
4		**3.2b** **3.3b**	83	99	>99:1
5		**3.2c** **3.3c**	78[f]	—[g]	—[g]
6		**3.2d** **3.3d**	94	98	99:1
7		**3.2e** **3.3e**	96	—[g]	98:2
8		**3.2f** **3.3f**	96	—[g]	99:1
9		**3.2g** **3.3g**	52	85	99:1
10		**3.2h** **3.3h**	37	71	98:2

[a] Reactions were performed using 2 equiv of NEt_3 in 0.125 M H_2O/DMF (3:2). [b] Reactions were performed using 2 equiv of K_3PO_4 in 0.125 M H_2O/dioxane (3:2). [c] The diastereoselectivity was the same for M = BF_3K and BMIDA and was determined by HPLC comparison to authentic diastereomers.[25] [d] Reactions were set up in a fumehood using Schlenk technique. [e] Reactions were performed using 1.2 equiv of boron reagent. [f] Yields were determined by ^1H NMR relative to an external standard. [g] Yield or diastereoselectivity was not determined.

While sequential addition of more trifluoroborate resulted in improved yields, we sought to develop a more efficient and practical process. We envisioned that higher yields could potentially be achieved via the slow-release of boronic acids from MIDA boronates (Table 3.4). The optimal conditions for the Rh(I)-catalyzed addition of trifluoroborates, which utilize triethylamine as the base, were not effective for MIDA boronates (entry 2). It is known that K_3PO_4 in 1:5 H_2O/dioxane promotes the continuous release of boronic acids over approximately 3 h.[17] Fortunately, K_3PO_4 was previously established to be a compatible base for the Rh(I)-catalyzed addition of trifluoroborates (entry 7, Table 3.1) and proved to be competent for MIDA boronates as well (entry 3, Table 3.4). While dioxane is a poor cosolvent for the trifluoroborate-mediated transformation, it resulted in higher yields for the MIDA boronate (entry 4). Similarly to the trifluoroborates, it was important to maintain the heterogeneous reaction conditions by having a solvent system composed of a minimum of 60% water (entry 5).[26] We also confirmed that the slow release of boronic acids is much more effective than simply using two equivalents of boronic acid in the Rh-catalyzed alkenylation reaction (entry 6).

Table 3.4. Optimization of reaction conditions for the addition of MIDA boronates



entry	M	base	solvent system	yield (%)[a,b]
1	BF_3K	NEt_3	H_2O/DMF (3:2)	53
2	BMIDA	NEt_3	H_2O/DMF (3:2)	17
3	BMIDA	K_3PO_4	H_2O/DMF (3:2)	61
4	BMIDA	K_3PO_4	H_2O/dioxane (3:2)	86
5	BMIDA	K_3PO_4	H_2O/dioxane (1:5)	60
6	$B(OH)_2$	K_3PO_4	H_2O/dioxane (3:2)	21

[a] Reaction conditions: 1 equiv of **3.2g**, 2 equiv of **3.1a** or **3.4a** or **3.5a**, 2.5 mol% $[Rh(OH)(cod)]_2$, 5.0 mol% dppbenz, 2 equiv NEt_3 or K_3PO_4, 0.125M in 2:3 H_2O/co-solvent, 60 ºC, 20 h. [b] Yields were determined by ^1H NMR relative to an external standard.

Scope in N-Sulfinyl Aromatic Aldimine for the Addition of Alkenyl MIDA Boronates

Encouraged by these results, we evaluated the MIDA boronate slow-release method with a variety of *N*-sulfinyl aromatic imines (Table 3.3). For the Rh(I)-catalyzed alkenylation of *N*-*tert*-butanesulfinyl aromatic aldimines, MIDA boronates performed better than the trifluoroborates. The Rh(I)-catalyzed addition of pentenyl MIDA boronate to electron neutral (entries 1 and 4) and deficient (entry 6) *N*-sulfinyl imines, provided the corresponding allylic amines in nearly quantitative yield and excellent diastereoselectivities. Notably, the most dramatic improvements in yield were achieved for the addition to electron-rich imines (entries 9-10).

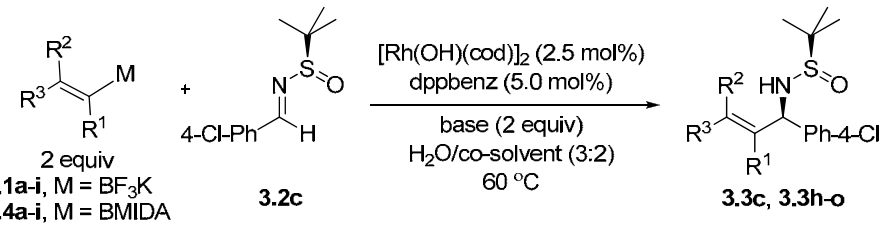
It is important to note that the $[Rh(OH)(cod)]_2$ precatalyst and dppbenz ligand are air stable, and therefore the alkenylation reactions can be set up using standard Schlenk techniques without requiring the use of an inert atmosphere box (Table 3.3, entry 2). Moreover, the equivalents of boron reagent **3.1a** or **3.4a** could be reduced without appreciably affecting the efficiency of the reaction (entry 3). With 1.2 equivalents of boron reagent, a minor decrease in yield was observed for the addition of the trifluoroborate and the reaction yield was essentially the same for the MIDA boronate.

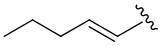
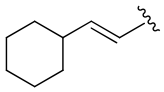
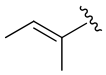
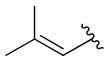
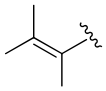
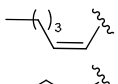
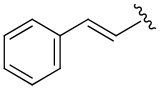
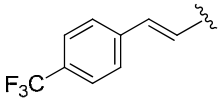
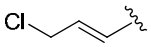
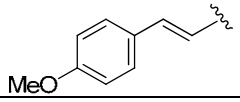
Scope in Organoboron Reagent for the Addition to N-Sulfinyl Aromatic Aldimines

The scope of the organoboron coupling partner was evaluated with *N*-sulfinyl 4-chlorobenzaldimine under the standard set of conditions (Table 3.5). We found that the Rh(I)-catalyzed alkenylation was not especially sensitive to substitution on the alkene, with the addition of di- (entries 1-2), tri- (entries 3-5), and tetra-substituted (entry 6) alkenyl trifluoroborates all proceeding in good yields and with high selectivities. While increased alkene substitution resulted in moderate decreases in yield for the trifluoroborates, the MIDA boronates maintained excellent yields (entries 4 and 6). Cis-substituted alkenyl trifluoroborates are also competent coupling partners and proceed with minimal or no olefin isomerization at short reaction times (entries 5 and 7).

We were also interested in examining how the electronics of the boron coupling partner affect the efficiency of the reaction. The alkenylation was found to be strongly influenced by electronics with the additions of electron-deficient trifluoroborates proceeding in lower yield (entries 8-10) than the additions of electron-rich trifluoroborates (entry 11). Although cinnamyl MIDA boronate **3.4h** added in significantly higher yield than the corresponding trifluoroborate (entry 8), the addition of the highly electron-deficient trifluoromethyl MIDA boronate **3.4i** proceeded in low yield (entry 10).[27] Electron-poor boron reagents are known to be less nucleophilic and undergo transmetallation at a slower rate in addition to being prone to homocoupling.[28] The unsuccessful addition of trifluoroborate **3.3q** could also be a result of competitive π-allyl rhodium formation with the allyl chloride moiety (entry 9).

Table 3.5. Scope in trifluoroborate and MIDA boronate for the addition to *N*-sulfinyl aromatic imines



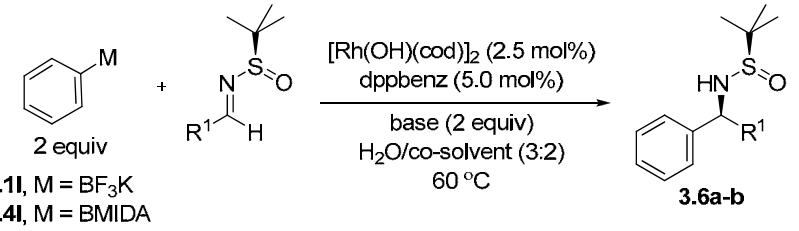
entry	organoboron reagent **3.1**/**4**		**3.3**	M = BF_3K[a] isolated yield (%)	BMIDA[b] isolated yield (%)	dr[c]
1		**3.1**/**4a**	**3.3d**	94	98	99:1
2		**3.1**/**4b**	**3.3i**	91	–[d]	99:1
3		**3.1**/**4c**	**3.3j**	97	–[d]	96:4
4		**3.1**/**4d**	**3.3k**	70	93	98:2
5[e]		**3.1**/**4e**[f]	**3.3l**	87	–[d]	–[d]
6		**3.1**/**4f**	**3.3m**	75	85	99:1
7[g]		**3.1**/**4g**	**3.3n**	91	–[d]	98:2
8		**3.1**/**4h**	**3.3o**	66	91	99:1
9		**3.1**/**4i**	**3.3p**	22	14	99:1
10[h]		**3.1**/**4j**	**3.3q**	0	–[d]	–[d]
11		**3.1**/**4k**	**3.3r**	91	–[d]	99:1

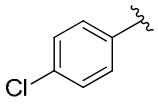
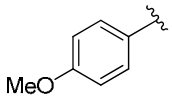
[a] Reactions were performed using 2 equiv of NEt_3 in 0.125 M H_2O/DMF (3:2). [b] Reactions were performed using 2 equiv of K_3PO_4 in 0.125 M H_2O/dioxane (3:2). [c] Diastereoselecitivity was the same for M = BF_3K and BMIDA and was determined by HPLC comparison to authentic diastereomers.[25] [d] Yield or diastereoselectivity was not determined. [e] Reaction was run for 1h to minimize isomerization (Z/E 91:9) and yield was determined by ^1H NMR relative to an external standard. [f] Trifluoroborate starting material was 96:4 *Z*/*E*. [g] Reaction was run for 1h to avoid isomerization (*Z*/*E* 99:1). [h] Reaction was performed with imine **3.2l**.

The conditions developed for the alkenylation proved to also be applicable to the arylation of *N*-*tert*-butanesulfinyl imines. The Rh(I)-catalyzed addition of aryl boron reagents to both electron deficient and rich *N*-sulfinyl aromatic imines **3.2d** and **3.2g**, respectively,

proceeded with high selectivity and yields for the MIDA boronates (Table 3.6).[29] Whereas the diastereoselectivity was found to be identical for MIDA boronates and trifluoroborates in the alkenylation reaction, a noticeable difference was observed in the arylation reaction with the MIDA boronate additions proceeding with higher selectivity. The yield and selectivity for the addition of phenyl MIDA boronate **3.4l** to electron-rich *N*-*tert*-butanesulfinyl 4-methoxybenzaldimine are significantly higher than those previously reported for the addition of phenylboronic acid.[30]

Table 3.6. Additions of aryl boron reagents to *N*-sulfinyl imines



entry	imine **3.2**	**3.6**	M	yield (%)[a]	dr[b]
1	 **3.2d**	**3.6a**	BF_3K[c]	84	96:4
2			BMIDA[d]	97	98:2
3	 **3.2g**	**3.6b**	BF_3K[c]	50	94:6
4			BMIDA[d]	89	98:2

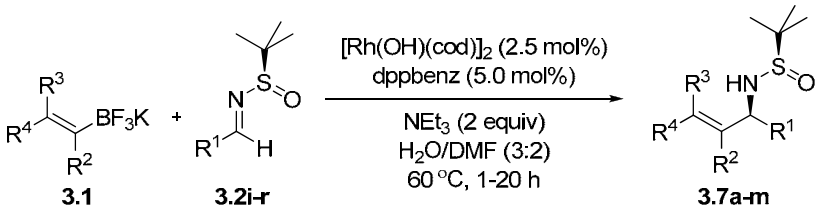
[a] Isolated yield after chromatography. [b] Diastereoselectivity was determined by HPLC comparison to authentic diastereomers.[25] [c] Reactions were performed using 2 equiv of NEt_3 in 0.125 M H_2O/DMF (3:2). [d] Reactions were performed using 2 equiv of K_3PO_4 in 0.125 M H_2O/dioxane (3:2).

Scope in N-Sulfinyl Aliphatic Aldimine for the Addition of Alkenyl Trifluoroborates and MIDA Boronates

Significantly, the scope of the Rh(I)-catalyzed addition of trifluoroborates could be extended to aliphatic imines (Table 3.7). Unbranched (entries 1-3) and δ-branched (entries 4-5) *N*-sulfinyl imines provided the corresponding allylic amines in good yields and high selectivities. The alkenylation of both β- (entry 6) and α-branched (entry 7) *N*-sulfinyl imines were successful albeit in somewhat reduced yield due to competitive imine hydrolysis. However, no reaction was observed with the sterically hindered *N*-sulfinyl imines **3.2p** and **3.2q** (entries 8-9). A moderate yield was obtained for the *N*-sulfinyl imine derived from phenyl acetaldehyde, which is typically a challenging substrate due to its facility for imine tautomerization (entry 10).

A limited exploration of the scope of the organotrifluoroborate coupling partner was carried out with aliphatic *N*-sulfinyl imines (Table 3.7). Trifluoroborates with branched aliphatic β–substituents (entry 11) and cis-substitution (entry 12) added in good yield and excellent selectivity. As was observed for the aryl imines, the α-substituted trifluoroborate added in outstanding yield with a slight decrease in selectivity (entry 13).

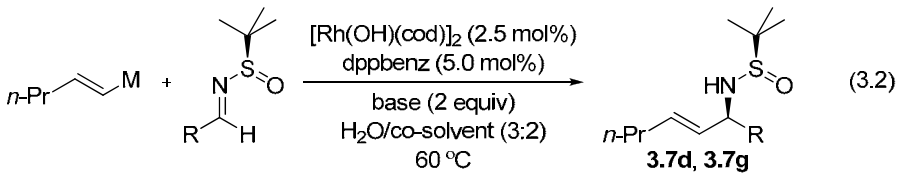
Table 3.7. Scope in *N-tert*-butanesulfinyl aliphatic imine with trifluoroborates



entry	trifluoroborate **1**	imine **3.2**		**3.7**	yield (%)[a]	dr[b]
1	**1a**		**3.2i**	**3.7a**	72	98:2
2	**1a**		**3.2j**	**3.7b**	62	98:2
3	**1a**		**3.2k**	**3.7c**	52	98:2
4	**1a**		**3.2l**	**3.7d**	78	99:1
5	**1a**		**3.2m**	**3.7e**	76	98:2
6	**1a**		**3.2n**	**3.7f**	64	98:2
7	**1a**		**3.2o**	**3.7g**	45	98:2
8	**1a**		**3.2p**	**3.7h**	0	
9	**1a**		**3.2q**	**3.7i**	0	
10	**1a**		**3.2r**	**3.7j**	44	97:3
11	**1b**		**3.2l**	**3.7k**	69	99:1
12[c]	**1f**		**3.2l**	**3.7l**	70	98:2
13	**1c**		**3.2l**	**3.7m**	90	95:5

[a] Isolated yields after chromatography. [b] Diastereoselectivity was determined by HPLC comparison to authentic diastereomers.[25] [c] Reaction was run for 1 h to minimize isomerization (*Z*/*E* 95:5).

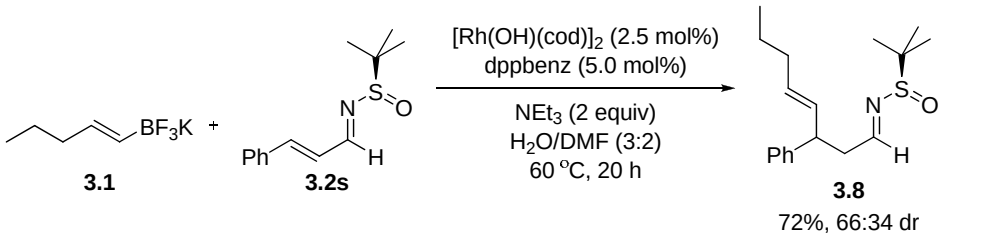
For *N*-sulfinyl imines **3.2** that are aliphatic, imine hydrolysis is the major side reaction competing with the alkenylation reaction. Consequently, this substrate class does not benefit from the slow-release of boronic acids from MIDA boronates. For non-hindered aliphatic imines, MIDA boronates resulted in the same yield as trifluoroborates (eq 3.2). However, for sterically hindered aliphatic imines, the addition of the MIDA boronate resulted in a lower yield.



(3.2)

3.7d, R = $PhCH_2CH_2$ *78%* (M = BF_3K), *79%* (M = BMIDA), 99:1 dr
3.7g, R = Cy *45%* (M = BF_3K), *21%* (M = BMIDA), 98:2 dr

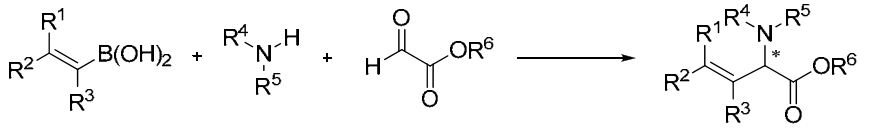
The addition of pentenyl trifluoroborate to *N*-sulfinyl α,β-unsaturated imine **3.2s** resulted in exclusively 1,4-addition (eq 3.3). While the reaction proceeded in good yield, the diastereoselectivity observed was poor. These results are consistent with the previously reported 1,4-addition of a copper reagent, which also proceeded in poor diastereoselectivity.[31] On the other hand, additions of other reagents, such as Grignards or lithiates, to *N*-sulfinyl α,β-unsaturated aldimines generally result in 1,2-addition.[32]



(3.3)

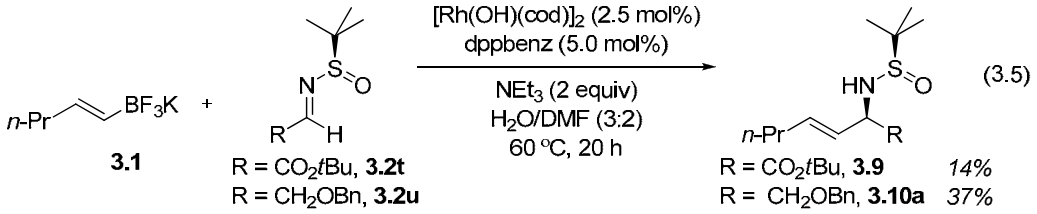
Diastereoselective Addition of Alkenyl Trifluoroborates to N-Sulfinyl Imino Esters and Ethers

The asymmetric addition of alkenyl trifluoroborates to *N-tert*-butanesulfinyl imino esters would provide a rapid entry into chiral α-amino acids. This class of compounds can also be prepared via the Petasis reaction, which is a multicomponent condensation of boronic acids with amines and glyoxylates (eq 3.4). The Petasis reaction of alkenyl boronic acids has recently been rendered asymmetric. Petasis and coworkers showed a single diastereoselective example that used (*R*)-2-glycinol as the amine in the reaction and source of diastereoinduction.[33] Schaus and coworkers elegantly rendered the Petasis reaction asymmetric through the use of chiral biphenols. [34] Their work was limited, however, to dialkyl amines.



(3.4)

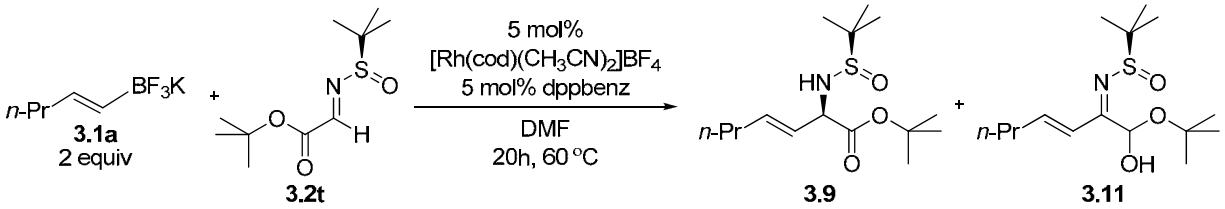
In an effort to further extend the scope of our alkenylation methodology, the addition of alkenyl trifluoroborates to *N-tert*-butanesulfinyl imino esters and ethers was briefly explored. These classes of imines are highly susceptible to hydrolysis and therefore the addition of pentenyl trifluoroborate using the standard basic aqueous conditions resulted in low yields of the desired α-branched allylic amines (eq 3.5).



(3.5)

After screening several reaction conditions, it was determined that water and base additives were not necessary for the addition of alkenyl trifluoroborates to *N*-sulfinyl imino esters (Table 3.8). On the contrary, the addition of 4Å molecular sieves was found to be essential for achieving high conversion (entries 1-3). A cationic rhodium catalyst in dry DMF provided the desired ester product in high yield (entry 3). Unfortunately, the reaction outcome was found to be inconsistent with varying amounts of **3.11** forming under seemingly identical reaction conditions. Byproduct **3.11** was the major product upon scaling up the reaction (entry 4).

Table 3.8. Optimization of reaction conditions for the addition to *N*-sulfinyl imino esters



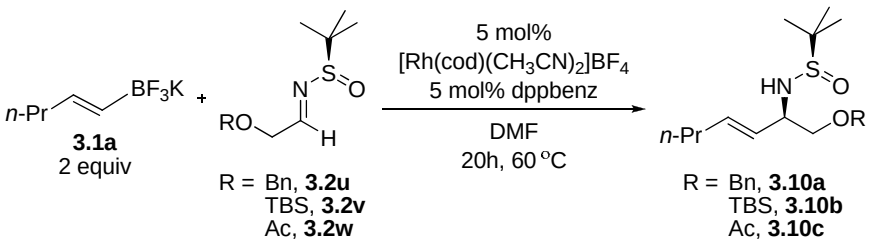
entry	additive	scale (mmol)	yield of **3.9** (%)[a]	yield of **3.11** (%)[a]	dr[b]
1	2% H_2O	0.063	2	0	-[c]
2	none	0.063	11	7	-[c]
3	4Å MS	0.063	74	15	94:6
4	4Å MS	0.250	28[d]	34[d]	95:5

[a] Yields were determined by ^{1}H NMR relative to an external standard. [b] Diastereoselectivity was determined by HPLC comparison to authentic diastereomers.[25] [c] Diastereoselectivity was not determined. [d] Isolated yields after chromatography.

The anhydrous conditions that were developed for *N*-sulfinyl imino ester **3.2t** proved to also be effective for the alkenylation of benzyl ether substrate **3.2u** (Table 3.9). However, these anhydrous conditions resulted in varying results (entry 1). We hypothesized that a small quantity of water was necessary for this transformation and were pleased to find that the addition of 2% water resulted in a reproducible transformation (entry 2). Various amounts of methanol (2-50%) as a protic additive were also investigated but this resulted in lower yields (19-49%). Switching the protecting group to a TBS resulted in a higher yield but partial deprotection of the TBS group was observed under the reaction conditions (entry 3). The TBS group also did not improve upon the moderate diastereoselectivity. Alkenylation of the acyl-protected ether **3.2w**, however, resulted in higher diastereoselectivity presumably due to the decreased coordinating ability of an acyl protected alcohol.

These promising initial results suggest that further exploration of the alkenylation of *N*-*tert*-butanesulfinyl imino esters and ethers is a worthwhile pursuit.

Table 3.9. Optimization of reaction conditions for the addition to *N*-sulfinyl imino ethers



entry	additive	R	yield (%)[a]	dr[b]
1	4Å MS	OBn	22-69	-[c]
2	2% H_2O	OBn	63	91:9
3	2% H_2O	OTBS	77[d]	88:12
4	2% H_2O	OAc	64	96:4

[a] Yields were determined by ^{1}H NMR relative to an external standard. [b] Diastereoselectivity was determined by HPLC comparison to authentic diastereomers.[25] [c] Diastereoselectivity was not determined. [d] 33% of this material was deprotected.

Determination of the Sense of Induction and Stereochemical Model

The absolute stereochemistry of the Rh(I)-catalyzed alkenylation was confirmed by single X-ray diffraction. The stereochemistry observed is consistent with delivery opposite the *t*-butyl group via an open transition-state (Figure 3.1). This is the same sense of induction that has been observed for other rhodium-catalyzed additions of boron reagents to *N*-sulfinyl imines and opposite that of Grignard additions to *N*-sulfinyl imines, which proceed via a closed transition state.[5i]

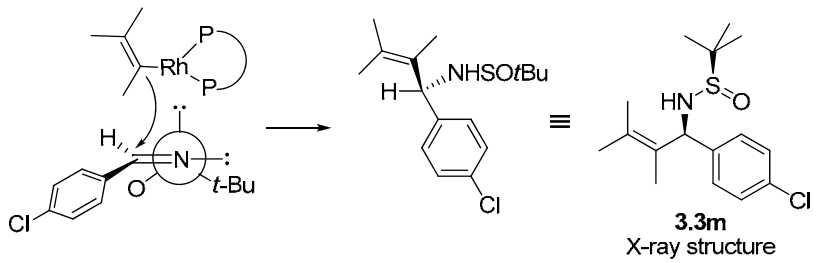


Figure 3.1. Stereochemical model for the Rh-catalyzed alkenylation.

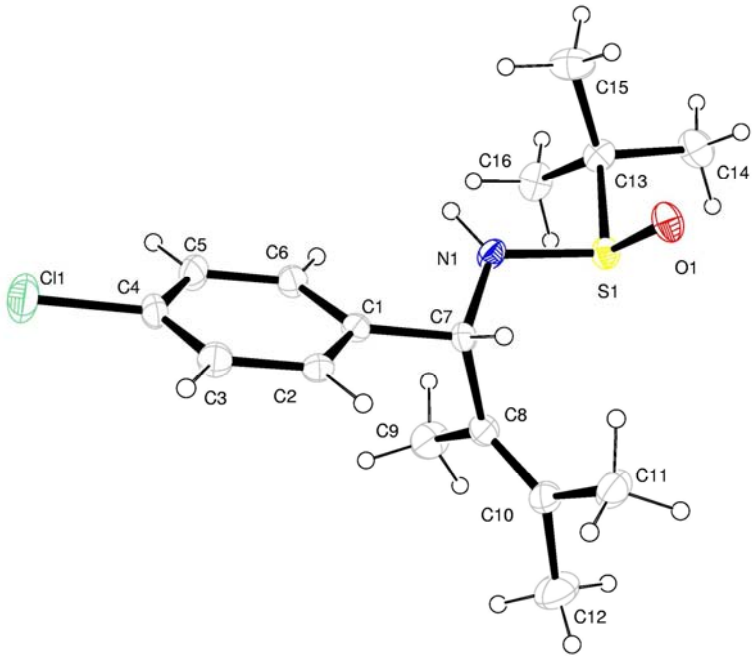
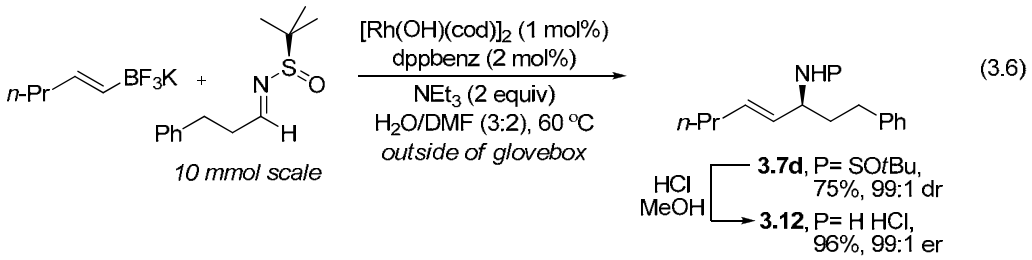


Figure 3.2. X-ray crystal structure of **3.3m** with thermal ellipsoids drawn at the 50% probability level.

Scale-Up and Cleavage of Sulfinyl Group

The further demonstrate the robustness of the method, the addition of pentenyl trifluoroborate **3.1a** to aliphatic *N*-sulfinyl imine **3.2l** was carried out on 10 mmol scale with 1 mol% of the rhodium catalyst using standard Schlenk techniques (eq 3.6). Analytically pure material was obtained in good yield and high selectivity. Furthermore, cleavage of the *tert*-butanesulfinamide group proceeded in high yield with no loss in stereochemical purity.



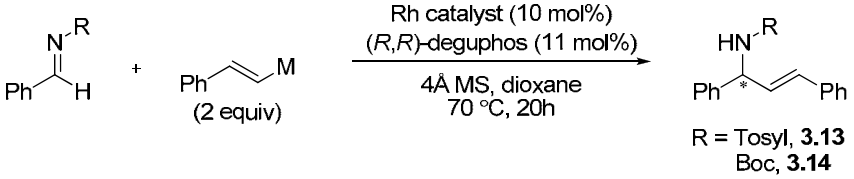
(3.6)

Enantioselective Addition of Alkenyl Boron Reagents to Activated Aldimines

A preliminary investigation into the enantioselective rhodium-catalyzed addition of alkenylboron reagents to activated imines was carried out. We began by evaluating the reaction between *N*-tosyl and *N*-Boc protected imines and cinnamyl boronic acid (Table 3.10). When the optimal conditions for the enantioselective addition of arylboronic acids to *N*-tosyl,[3i] *N*-Boc,[3h] and *N*-phosphinoyl[3c] imines were applied to the alkenylation of *N*-tosyl and *N*-Boc benzaldimine,

low yields and enantioselectivities were observed (entries 1-2). A significant increase in yield was observed upon switching to a cationic rhodium catalyst and a trifluoroborate coupling partner (entries 3-4). While these newly developed conditions resulted in the addition of cinnamyl trifluoroborate to both *N*-tosyl and *N*-Boc benzaldimine in good yields, the transformations took place without much selectivity.

Table 3.10. Optimization of reaction conditions for the enantioselective alkenylation of *N*-Boc and *N*-tosyl benzaldimine

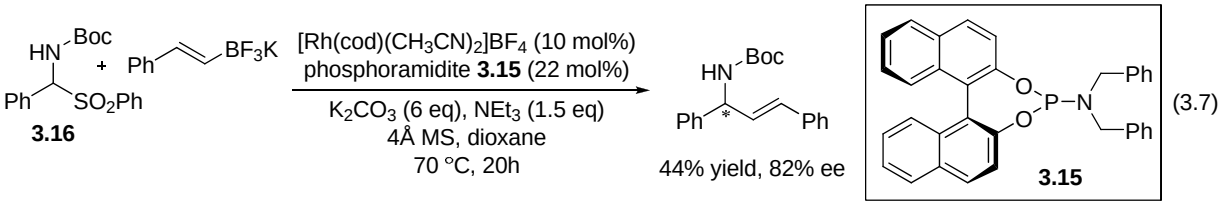


entry	R	Rh catalyst	M	yield (%)[a]	ee (%)[b]
1[c]	tosyl	$[Rh(acac)(coe)_2]$,	$B(OH)_2$	10	36
2[c]	Boc	$[Rh(acac)(coe)_2]$	$B(OH)_2$	14	6
3	tosyl	$[Rh(cod)(CH_3CN)_2]BF_4$	BF_3K	73	4
4	Boc	$[Rh(cod)(CH_3CN)_2]BF_4$	BF_3K	71	6

[a] Isolated yields after chromatography. [b] Enantioselectivity was determined by HPLC on a chiral stationary phase. [c] Reactions were performed using 1 equiv of NEt_3.

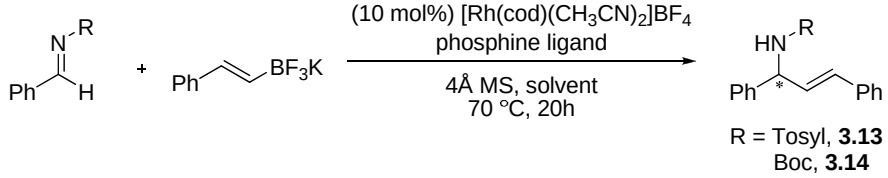
A wide variety of commercially available chiral bisphosphines were screened next in the hope of improving the enantioselectivity (Table 3.11). Unfortunately, all of these bisphosphine ligands resulted in low enantioselectivity (entries 1-7). A monodentate phosphoramidite ligand **3.15**, however, provided allylic amine **3.14** in high yield and with a promising level of enantioselectivity (entries 8-9). Phosphoramidite ligands are highly modular and easy to synthesize.[3e] Unfortunately, after screening many different phosphoramidite, phosphite and amidophosphane ligands, no further improvements in enantioselectivity were observed. Upon switching the protecting group from tosyl to Boc, however, the optimal phosphoramidite ligand conditions provided the product in 76% ee (entry 10). Changing the solvent from dioxane to DMF, resulted in nearly quantitative conversion but lower enantioselectivity (entry 11).

Significantly, the optimal conditions resulted in the successful enantioselective addition of cinnamyl trifluoroborate to *N*-Boc benzaldimine generated in situ from the stable and easily prepared α–carbamoyl sulfone **3.16** (eq 3.7). These promising initial results suggest further exploration of the scope of the enantioselective alkenylation is merited.



(3.7)

Table 3.11. Phosphine ligand screen for the enantioselective alkenylation of *N*-tosyl and *N*-Boc benzaldimine



entry	R	solvent	chiral ligand	yield (%)[a]	ee (%)[b]
1	tosyl	dioxane	(*R*,*R*)-deguphos (11 mol %)	69	4
2	tosyl	dioxane	(*R*,*R*)-*i*Pr-DUPHOS (11 mol %)	24	3
3	tosyl	dioxane	(*R*)-BINAP (11 mol %)	71	3
4	tosyl	dioxane	(*R*,*R*)-DIOP (11 mol %)	48	16
5	tosyl	dioxane	Walphos (11 mol %)	8	20
6	tosyl	dioxane	(*R*,*R*)-QuinoxP (11 mol %)	53	16
7	tosyl	dioxane	(*R*,*R*)-DIPAMP (11 mol %)	26	2
8	tosyl	dioxane	phosphoramidite **3.15** (11 mol %)	81	20
9	tosyl	dioxane	phosphoramidite **3.15** (22 mol %)	70	50
10	Boc	dioxane	phosphoramidite **3.15** (22 mol %)	51	76
11	Boc	DMF	phosphoramidite **3.15** (22 mol %)	97	53

[a] Yields were determined by ^{1}H NMR relative to an external standard. [b] Enantioselectivity was determined by HPLC on a chiral stationary phase.

Conclusion

The development of the first asymmetric, Rh-catalyzed addition of alkenylboron reagents to imines was described. The addition of alkenyl trifluoroborates to both aromatic and aliphatic *N*-*tert*-butanesulfinyl imines proceeds with very high selectivity and with broad substrate scope in both the imine and trifluoroborate. Reaction conditions were also identified that simultaneously promote the Rh-catalyzed addition and slow-release of boronic acids, thereby allowing MIDA boronates to be used directly as addition reagents to *N*-*tert*-butanesulfinyl imines. By minimizing decomposition of the boron reagent, the efficient addition of MIDA boronates to aromatic *N*-*tert*-butanesulfinyl imines resulted in impressive yields for many imine and boron substrates. Reaction conditions were also identified for the addition of alkenyl trifluoroborates to hydrolytically labile *N*-tert-butanesulfinyl imino ethers and esters. This practical and general method enables the asymmetric synthesis of α-branched allylic amines from stable and easily accessible *N*-sulfinyl imine and trifluoroborate or MIDA boronate starting materials.

Furthermore, promising initial results have been obtained for the enantioselective addition of cinnamyl trifluoroborates to *N*-Boc and *N*-tosyl aromatic imines. Evaluation of the scope of this methodology would be a worthwhile pursuit.

Experimental Section

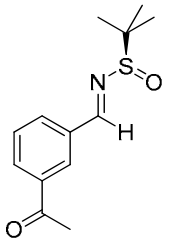
General methods. Unless otherwise noted, all catalytic alkenylation reactions were assembled in a nitrogen-filled Vacuum Atmospheres inert atmosphere box and carried out in Kimble 5 mL microvials (Kimble product number 60700-5) using PTFE stir-vanes (Kimble product number 749060-0003) and capped with mini-inert seals (Kimble product number 749110-0022) and blue nylon caps (Kimble product number 410119-2015). The reaction vials were heated in a custom-made aluminum heating block drilled to fit the vials (UC machine shop) and the temperature was maintained by placing the block on an IKA stirrer/hot plate (RCT basic model) with a thermistor controller (ETS-D4 fuzzy). Flash column chromatography was carried out either with Merck 60 230-240 mesh silica gel, or using a Biotage SP Flash Purification System (Biotage No. SP1-B1A) with Flash+ 3 cartridges (Biotage No. FPK0-1107-16046). Diastereoselectivity determinations were performed using an Agilent 1100 series LC equipped with a silica normal phase column (Microsorb Si 100 A packing) with a multiwavelength detector. ^{1}H, ^{13}C, ^{19}F NMR spectra were obtained on a Bruker AVB-400, AVQ-400, or DRX-500 at room temperature. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. ^{1}H resonances are referenced to either the residual solvent peak ($CDCl_3$, 7.26 ppm; acetone-d_6, 2.05 ppm; MeOD, 3.31 ppm) or TMS (0.00 ppm), ^{13}C resonances are referenced to the residual solvent peak ($CDCl_3$, 77.23 ppm; MeOD, 49.00 ppm), and ^{19}F resonances are referenced to $CFCl_3$ (0 ppm). IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer equipped with an attenuated total reflectance accessory and only partial data are listed. Melting points were determined on a Laboratory Devices Mel-Temp 3.0 and are reported uncorrected. Elemental analyses and mass spectrometry analyses were performed by the University of California at Berkeley Microanalysis and Mass Spectrometry Facilities.

General materials. Hydroxy(1,5-cyclooctadiene)rhodium(I) dimer, Chloro(1,5-cyclooctadiene)rhodium(I) dimer, and 1,2-bis(diphenylphosphino)benzene were purchased from Strem and used without further purfication. $[Rh(cod)(MeCN)_2]BF_4$[35] was synthesized according to the literature procedure. (*R*)-*tert*-Butanesulfinamide was provided by AllyChem Co. Ltd (Dalian, China). 4 M HCl (solution in 1,4-dioxane) was purchased from Aldrich. *N*-sulfinyl imines **3.2a**[36], **3.2b**[37], **3.2d**[38], **3.2c**[39], **3.2e**[38], **3.2g**[36], **3.2h**[40], **3.2j**[41], **3.2k**[36], **3.2l**[42], **3.2o**[41], **3.2p**[43], **3.2r**[36], **3.2s**[44], **3.2t**[45], and **3.2u-v**[46] were synthesized according to the literature procedures. Trifluoroborate **3.1j** was synthesized according to literature procedure.[47] 1,4-Dioxane, tetrahydrofuran, and pentane were obtained from a Seca Solvent Systems by GlassContour (solvent dried over alumina under a N_2 atmosphere). Methanol and triethylamine were distilled under N_2 over CaH_2 immediately prior to use. Anhydrous *N*,*N*-dimethylformamide (water <50 ppm) was purchased from Acros and used without further purification. All liquid reagents and solvents were thoroughly degassed using three freeze-pump-thaw cycles prior to introduction to the glove box.

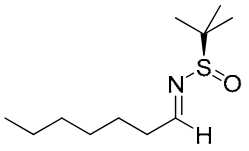
Synthesis of *N*-*tert*-Butanesulfinyl Imines

General synthesis for the synthesis of *N*-*tert*-butanesulfinyl imines 3.2 (Procedure A). This procedure was adapted from Ellman.[36] A solution of $Ti(OEt)_4$ (2.0 equiv) and aldehyde (1.0-1.2 equiv) in THF (0.5 M in aldehyde) was prepared under a N_2 atmosphere. Then, (*R*)-*tert*-

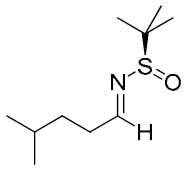
butanesulfinamide (1.0-1.2 equiv) was added. The reaction solution was stirred overnight at rt. While rapidly stirring, the reaction was quenched by adding an equal volume of brine. The mixture was diluted with EtOAc and stirred vigorously for 20 min. The resulting mixture was filtered through a pad of Celite, and the pad of celite was washed with EtOAc. The filtrate was transferred to a separatory funnel and washed with brine. The brine was then washed with a small amount of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The sulfinyl imines were purified by silica gel chromatography.



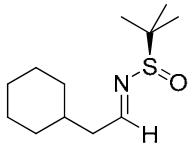
(*R*)-*N*-*tert*-butanesulfinyl 3-acetylbenzaldimine (3.2f). Procedure A was followed using 3-acetylbenzaldehyde (0.50 g, 3.4 mmol), $Ti(OEt)_4$ (1.4 mL, 6.7 mmol), and (*R*)-*tert*-butanesulfinamide (0.41 g, 3.4 mmol) in 6.7 mL of THF. Column chromatography (Biotage Flash+ cartridge, 7-60% EtOAc/hexanes) afforded 0.55 g (65% yield) of **3.2f** as a clear oil that solidified upon storage at -20 ºC. mp 34.2-35.1 ºC. $[\alpha]_D^{23}$ −100.9º (*c* 1.0, $CHCl_3$). IR 2973, 1685, 1602, 1356, 1074 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 9H), 2.76 (s, 3H), 7.59 (t, 1H, *J* = 7.8), 8.04 (dt, 1H, *J* = 7.8, 1.6), 8.10 (dt, 1H, *J* = 7.8, 1.6), 8.39 (t, 1H, *J* = 1.6 Hz), 8.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 26.9, 58.2, 129.3, 129.6, 132.0, 133.7, 134.6, 138.0, 162.1, 197.4. MS (ESI): *m/z* 252 $[MH]^+$. Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.05; H, 6.73; N, 5.50.



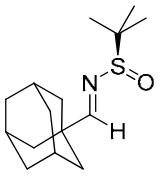
(*R*)-*N*-*tert*-butanesulfinyl heptaldimine (3.2i). Procedure A was followed using heptanal (1.71 g, 15.0 mmol), $Ti(OEt)_4$ (6.3 mL, 30 mmol), and (*R*)-*tert*-butanesulfinamide (2.18 g, 18.0 mmol) in 30 mL of THF. Column chromatography (SiO_2, 10-30% EtOAc/hexanes) afforded 1.63 (50% yield) of **3.2i** as a clear oil. $[\alpha]_D^{23}$ −256.7º (*c* 1.0, $CHCl_3$). IR 2926, 1621, 1362, 1085 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.0), 1.18 (s, 9H), 1.22-1.39 (m, 6H), 1.60 (quint, 2H, *J* = 7.5), 2.46-2.53 (m, 2H), 8.05 (t, 1H, *J* = 4.5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 22.5, 22.7, 25.7, 29.1, 31.7, 36.3, 56.7, 170.0. MS (ESI): *m/z* 218 $[MH]^+$. Anal. Calcd for $C_{11}H_{23}NOS$: C, 60.78; H, 10.66; N, 6.44. Found: C, 60.47; H, 10.67; N, 6.24.



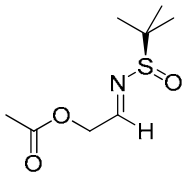
(*R*)-*N*-*tert*-butanesulfinyl 4-methylpentanaldimine (3.2m). Procedure A was followed using 4-methylpentanal[48] (0.99 g, 9.9 mmol), $Ti(OEt)_4$ (4.2 mL, 17 mmol), and (*R*)-*tert*-butanesulfinamide (1.00 g, 8.25 mmol) in 20 mL of THF. Column chromatography (SiO_2, 15-20% EtOAc/hexanes) afforded 1.61 (96% yield) of **3.2m** as a clear oil. $[\alpha]_D^{23}$ −274.2º (*c* 1.0, $CHCl_3$). IR 2956, 1621, 1363, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, 6H, *J* = 6.8), 1.20 (s, 9H), 1.48-1.54 (m, 2H), 1.62 (nonet, 1H, *J* = 6.4), 2.50-2.55 (m, 2H), 8.07 (t, 1H, *J* = 4.8). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 22.3, 27.7, 34.1, 34.4, 56.5, 169.9. MS (FAB): *m/z* 204 $[MH]^+$. Anal. Calcd for $C_{10}H_{21}NOS$: C, 59.07; H, 10.41; N, 6.89. Found: C, 59.00; H, 10.55; N, 6.62.



(*R*)-*N*-*tert*-butanesulfinyl 2-cyclohexylacetaldimine (3.2n). Procedure A was followed using 2-cyclohexylacetaldehyde[49] (0.57 g, 4.5 mmol), $Ti(OEt)_4$ (1.9 mL, 9.1 mmol), and (*R*)-*tert*-butanesulfinamide (0.66 g, 5.5 mmol) in 9 mL of THF. Column chromatography (SiO_2, 20% EtOAc/hexanes) afforded 0.82 (78% yield) of **3.2n** as a clear oil. $[\alpha]_D^{23}$ −270.9º (*c* 1.0, $CHCl_3$). IR 2863, 1596, 1331, 1060 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.92-1.08 (m, 2H), 1.10-1.35 (m, 3H), 1.19 (s, 9H), 1.60-1.81 (m, 6H), 2.40 (t, 2H, *J* = 5.7), 8.05 (t, 1H, *J* = 5.4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.6, 26.25, 26.26, 26.3, 33.41, 33.45, 35.7, 43.9, 56.7, 169.7. MS (ESI): *m/z* 230 $[MH]^+$. Anal. Calcd for $C_{12}H_{23}NOS$: C, 62.83; H, 10.11; N, 6.11. Found: C, 62.51; H, 10.20; N, 6.16.



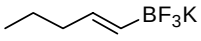
(*R*)-*N*-*tert*-butanesulfinyl adamantane-1-aldimine (3.2q). Procedure A was followed using crude adamantane-1-carbaldehyde[50] (1.3 g, 7.9 mmol), $Ti(OEt)_4$ (3.3 mL, 16 mmol), and (*R*)-*tert*-butanesulfinamide (1.2 g, 9.5 mmol) in 16 mL of THF. Column chromatography (Biotage Flash+ cartridge, 2-40% EtOAc/hexanes) afforded 1.1 g (44% yield) of **3.2q** as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 1.18 (s, 9H), 1.61 (s, 3H), 1.68-1.81 (m, 9H), 2.06 (br s, 3H), 7.77 (s, 1H).



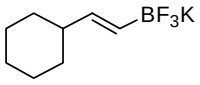
(*R*)-Acyloxyethylidene-*N*-*tert*-butanesulfinamide (3.2w). To a 0.5 M solution of (R_S)-*tert*-butanesulfinamide (2.02 g, 16.7 mmol) in CH_2Cl_2 was added anhydrous $CuSO_4$ (4.7 g, 29.4 mmol) and crude acetoxyacetaldehyde[51] (1.0 g, 9.8 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed with CH_2Cl_2 and the filtrate concentrated. Column chromatography (Biotage Flash+ cartridge, 2-40% EtOAc/hexanes) afforded 0.65 g (32% yield) of **3.2w**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H), 2.15 (s, 3H), 4.89 (dd, 1H, 2.8, 16.4), 5.00 (dd, 1H, *J* = 2.8, 16.4), 8.00 (t, 1H, *J* = 2.8). HRMS-ESI (m/z): $[MH]^+$ calcd for $C_8H_{16}NO_3S$, 206.0845; found, 206.0845.

Synthesis of Alkenyl Trifluoroborates

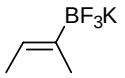
General procedure for the synthesis of alkenyl trifluoroborates 3.1 (Procedure B). This procedure was adapted from Molander.[52] The boronic acid (1 equiv) was dissolved in a minimal amount of MeOH and cooled to 0 ºC. A 4.5 M solution of KHF_2 (3.5 equiv) in water was added dropwise and the reaction mixture was stirred for 1 h at 0 ºC. The reaction mixture was frozen and lyophilized. The dried solids were then triturated with hot acetone and filtered to remove inorganic salts. The resulting filtrate was concentrated and redissolved with heating in a minimal amount of acetone. After addition of Et_2O and filtration of the precipitate, the trifluoroborate product was obtained as a white solid.



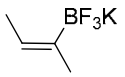
Potassium (*E*)-1-pentenyltrifluoroborate (3.1a). Procedure B was followed using commercialy available (*E*)-1-penten-1-ylboronic acid. ^{1}H NMR (400 MHz, acetone-d_6): δ 0.85 (t, 3H, *J* = 7.4), 1.32 (sextet, 2H, *J* = 7.4), 1.86-1.94 (m, 2H), 5.31-5.41 (m, 1H), 5.60-5.71 (m, 1H). ^{19}F NMR (376 MHz, acetone-d_6): δ -140.9 − -140.0 (m). MS (ESI): *m/z* 137 $[M-K]^-$. Anal. Calcd for $C_5H_9BF_3K$: C, 34.12; H, 5.15. Found: C, 34.07; H, 5.33.



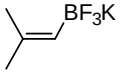
Potassium (*E*)-(2-cyclohexylvinyl)trifluoroborate (3.1b). Procedure B was followed using commercialy available (*E*)-(2-cyclohexylvinyl)boronic acid. ^{1}H NMR (400 MHz, acetone-d_6): δ 0.94-1.27 (m, 5H), 1.55-1.72 (m, 5H), 1.72-1.84 (m, 1H), 5.32 (dqd, 1H, *J* = 17.8, 3.6, 1.2), 5.62 (dd, 1H, *J* = 17.8, 6.0). ^{19}F NMR (376 MHz, acetone-d_6): δ -140.7 − -139.7 (m). MS (ESI): *m/z* 177 $[M-K]^-$. Anal. Calcd for $C_8H_{13}BF_3K$: C, 44.46; H, 6.06. Found: C, 44.12; H, 5.70.



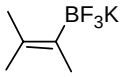
Potassium (2*Z*)-2-buten-2-yltrifluoroborate (3.1c). Procedure B was followed using (2*Z*)-2-buten-2-ylboronic acid.[53] ^{1}H NMR (400 MHz, acetone-d_6): δ 1.46 (d, 3H, J = 6.6), 1.49 (s, 3H), 5.45-5.55 (m, 1H). ^{19}F NMR (376 MHz, acetone-d_6): δ -145.9 − -144.9 (m). MS (ESI): *m/z* 123 [M-K]$^-$. Anal. Calcd for $C_4H_7BF_3K$: C, 29.66; H, 4.36. Found: C, 29.77; H, 4.31.



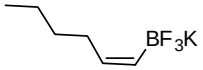
Potassium (2*E*)-2-buten-2-yltrifluoroborate (3.1e). Procedure B was followed using (2*E*)-2-buten-2-ylboronic acid[53] to afford trifluoroborate **3.1e** as a mixture of isomers (96:4 *E*/*Z*). ^{1}H NMR (400 MHz, acetone-d_6): δ 1.54 (s, 3H), 1.62 (d, 3H, J = 6.4), 5.21-5.38 (m, 1H). ^{19}F NMR (376 MHz, acetone-d_6): δ -138.2 − -137.7 (m). MS (ESI): *m/z* 123 [M-K]$^-$.



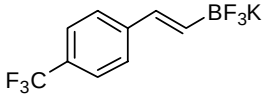
Potassium 2,2-dimethylethenyltrifluoroborate (3.1d). 2,2-Dimethylethenylboronic acid was prepared according to a procedure adapted from Gamsey.[53] 1-Bromo-2-methyl-1-propene (1.50 mL, 14.8 mmol) was dissolved in THF (15 mL), cooled to -78 ºC, and *t*-BuLi (1.7M in pentane, 19.2 mL, 32.6 mmol) was added dropwise. The bright yellow solution was stirred at -78 ºC for 1 h, and triisopropylborate (5.10 mL, 22.2 mmol) was then added. The reaction mixture was stirred at -78 ºC for 4 h and then warmed to 0 ºC over 2 h. Saturated NH_4Cl (15 mL) was added, and stirring was continued for 30 min at room temperature. The reaction mixture was extracted with Et_2O (2 x 30 mL). The organic portions were combined, washed with H_2O, and dried over $MgSO_4$. After filtration and concentration, 2,2-dimethylethenyl boronic was obtained as an off-white solid. Procedure B was then followed using the crude 2,2-dimethylethenyl boronic acid. ^{1}H NMR (400 MHz, acetone-d_6): δ 1.61 (s, 3H), 1.68 (s, 3H), 4.99-5.06 (m, 1H). ^{19}F NMR (376 MHz, acetone-d_6): δ -135.8 − -135.0 (m). MS (ESI): *m/z* 123 [M-K]$^-$. Anal. Calcd for $C_4H_7BF_3K$: C, 29.66; H, 4.36. Found: C, 29.83; H, 4.46.



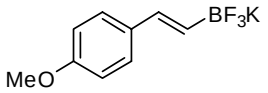
Potassium 3-methyl-2-buten-2-yltrifluoroborate (3.1f). Procedure B was followed using commercially available 3-methyl-2-buten-2-ylboronic acid. ^{1}H NMR (400 MHz, acetone-d_6): δ 1.49 (s, 3H), 1.50 (s, 3H), 1.73 (s, 3H). ^{19}F NMR (376 MHz, acetone-d_6): δ -137.2 − -136.4 (m). MS (ESI): *m/z* 137 [M-K]$^-$. Anal. Calcd for $C_5H_9BF_3K$: C, 34.12; H, 5.15. Found: C, 33.93; H, 4.97



Potassium (*Z*)-1-Hexenyltrifluoroborate (3.1g). (*1Z*)-2-Hex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]diaxaborolane[54] was converted to the trifluoroborate according to a procedure adapted from Molander.[55] (*1Z*)-2-Hex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1.04 g, 4.95 mmol) was dissolved in methanol (9.9 mL) and cooled to 0 ºC. A 4.5 M solution of potassium hydrogen fluoride (1.93 g, 24.5 mmol) in water was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. The methanol was removed by rotary evaporation and the water was removed by lyophilization. Extraction of the solid mixture with acetone (3 x 25 mL), followed by filtration (3x), afforded a solution of the product in acetone. The resulting filtrate was concentrated and redissolved in a minimal amount of acetone (~ 5 mL). Addition of Et_2O (~ 75 mL) and filtration of the precipitate, afforded 0.665 g (71% yield, 99:1 Z/E) of **3.1g** as a white solid. ^{1}H NMR (400 MHz, acetone-d_6): δ 0.86 (t, 3H, J = 7.0), 1.21-1.35 (m, 4H), 2.14-2.23 (m, 2H), 5.23-5.32 (m, 1H), 5.48-5.66 (m, 1H). ^{19}F NMR (376 MHz, acetone-d_6): δ -135.5 − -134.5 (m). MS (ESI): *m/z* 151 [M-K]$^-$. Anal. Calcd for $C_6H_{11}BF_3K$: C, 37.92; H, 5.83. Found: C, 37.98; H, 6.14.



Potassium (*E*)-2-[4-(trifluoromethyl)phenyl]trifluoroborate (3.1i). Procedure B was followed using commercially available (*E*)-2-[4-(trifluoromethyl)phenyl]vinylboronic acid. ^{1}H NMR (400 MHz, acetone-d_6): δ 6.52 (dq, 1H, J = 18.2, 3.4), 6.70 (d, 1H, J = 18.2), 7.50-7.58 (m, 4H). ^{19}F NMR (376 MHz, acetone-d_6): δ -141.8 − -141.1 (m, 1F), -61.6 (s, 3F). MS (ESI): *m/z* 239 [M-K]$^-$. Anal. Calcd for $C_9H_6BF_6K$: C, 38.88; H, 2.18. Found: C, 38.64; H, 2.05.

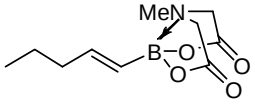


Potassium (*E*)-2-(4-methoxyphenyl)vinyltrifluoroborate (3.1k). Procedure B was followed using commercially available (*E*)-2-(4-methoxyphenyl)vinylboronic acid. ^{1}H NMR (400 MHz, acetone-d_6): δ 3.75 (s, 3H), 6.17 (dq, 1H, J = 18.2, 3.6), 6.57 (d, 1H, J = 18.2), 6.76-6.83 (m, 2H), 7.22-7.30 (m, 2H). ^{19}F NMR (376 MHz, acetone-d_6): δ -141.1 − -140.4 (m). MS (ESI): *m/z* 201 [M-K]$^-$. Anal. Calcd for $C_9H_9BF_3KO$: C, 45.03; H, 3.78. Found: C, 44.77; H, 3.74.

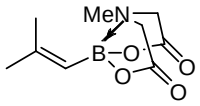
Synthesis of MIDA Boronates

General procedure for the synthesis of MIDA boronates 3.4 (Procedure C). This procedure was adapted from Burke.[17] To a round-bottom flask equipped with a stir bar was added the appropriate boronic acid (1 equiv), *N*-methyliminodiacetic acid (1.05 equiv), and 10:1 toluene:DMSO (0.02 M). The flask was fitted with a Dean-Stark trap and the Dean-Stark trap was fitted with a reflux condenser. The stirred mixture was heated to reflux with azeotropic removal of water for 18 h. The toluene (40 ºC, 30 mm Hg) and DMSO (40 ºC, 0.050 mm Hg)

were removed *in vacuo*. The resulting residue was adsorbed onto Celite *in vacuo* from an acetone suspension and the resulting powder was subjected to column chromatography (0-20% MeCN/Et_2O).



(*E*)-1-Pentenyl MIDA boronate (3.4a). Procedure C was followed using commercially available (*E*)-1-pentenylboronic acid (500 mg, 4.38 mmol), *N*-methyliminodiacetic acid (677 mg, 4.60 mmol), toluene (200 mL), and DMSO (20 mL) to afford 821 mg (83%) of **3.4a** as a white solid. IR 2957, 1748, 1643, 1461, 1289, 1119, 998, 856 cm^{-1}. ^1H NMR (600 MHz, acetone-d_6): δ 0.89 (t, 3H, J = 7.4), 1.42 (sextet, 2H, J = 7.4), 2.06-2.11 (m, 2H), 2.97 (s, 3H), 3.98 (d, 2H, J = 16.9), 4.17 (d, 2H, J = 16.9), 5.47 (dt, J = 17.6, 1.5), 6.08 (dt, J = 17.6, 6.5). ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 22.6, 38.2, 47.3, 62.1, 126.8 (br), 145.7, 169.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{10}H_{17}NO_4B$, 226.1245; found, 226.1248.



2,2-Dimethylethenyl MIDA boronate (3.4d). Dimethylethenylboronic acid was prepared immediately prior to conversion to the MIDA boronate. To a solution of trimethylborate (1.77 mL, 15.6 mmol) in THF (2.5 mL) cooled to -78 ºC, was added 2-methyl-1-propenylmagnesium bromide (25.0 mL, 0.5 M in THF, 12.5 mmol) over 30 min using an addition funnel. The reaction mixture was stirred at -78 ºC for 15 min and then warmed to room temperature with stirring for 1 h. After cooling the reaction mixture to 0 ºC, a 30% aqueous HCl solution (17.5 mL) was added, and the mixture was stirred for 1 h at 0 ºC and then 30 min at room temperature. The reaction mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to ~ 10 mL. To avoid decomposition of the boronic acid, it is important to avoid concentrating to dryness. Toluene (562 mL) and DMSO (62.5 mL) were then added, and the remaining Et_2O was removed (15 ºC, 30 mm Hg). *N*-methyliminodiacetic acid (1.93 g, 13.1 mmol) was added to the toluene/DMSO solution containing the crude 2,2-dimethylethenyl boronic acid and procedure C was followed to afford 1.81 g (68%, 2 steps) of **3.4d** as a white solid. IR 3010, 1743, 1647, 1450, 1288, 1140, 982, 867 cm^{-1}. ^1H NMR (600 MHz, acetone-d_6): δ 1.78 (d, 3H, J = 1.0), 1.81 (d, 3H, J = 1.3), 2.99 (s, 3H), 3.98 (d, 2H, J = 16.8), 4.15 (d, 2H, J = 16.8), 5.05-5.08 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1, 29.7, 47.0, 62.3, 121.1 (br), 149.6, 169.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_9H_{15}NO_4B$, 212.1092; found, 212.1089.

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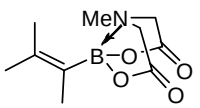
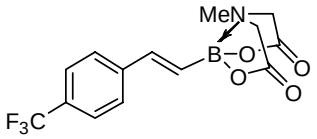


3-Methyl-2-buten-2-yl MIDA boronate (3.4f). Procedure C was followed using commercially available 3-methyl-2-buten-2-ylboronic acid (304 mg, 2.67 mmol), *N*-methyliminodiacetic acid (412 mg, 2.80 mmol), toluene (120 mL), and DMSO (12 mL) to afford

56 mg (9%) of **3.4f** as a white solid. IR 2914, 1743, 1627, 1454, 1335, 1284, 1156, 1022, 980, 859 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ 1.58 (s, 3H), 1.74 (s, 3H), 1.82 (s, 3H), 2.95 (s, 3H), 4.02 (d, 2H, J = 17.0), 4.20 (d, 2H, J = 17.0). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.1, 23.0, 23.7, 47.3, 63.4, 124.7 (br), 142.3, 169.2. HRMS-ESI (m/z): $[MNa]^+$ calcd for $C_{10}H_{16}NO_4BNa$, 248.1065; found, 248.1062.



(*E*)-2-[4-(Trifluoromethyl)phenyl] MIDA boronate (3.4i). Procedure C was followed using commercially available (*E*)-2-[4-(trifluoromethyl)phenyl]vinylboronic acid (398 mg, 1.84 mmol), *N*-methyliminodiacetic acid (284 mg, 1.93 mmol), toluene (184 mL), and DMSO (18.4 mL) to afford 570 mg (95%) of **3.4i** as a white solid. IR 3010, 1754, 1326, 1116, 1065, 993, 851 cm^{-1}. ^1H NMR (600 MHz, acetone-d_6): δ 3.09 (s, 3H), 4.13 (d, 2H, J = 16.9), 4.31 (d, 2H, J = 16.9), 6.57 (d, 1H, J = 18.2), 7.05 (d, 1H, J = 18.2), 7.68 (d, 2H, J = 8.3), 7.74 (d, 2H, J = 8.3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 47.5, 62.5, 125.4 (q, J = 270), 126.3 (q, J = 4.5), 128.0, 129.5 (br), 129.8 (q, J = 31.5), 141.3, 143.0, 169.1. ^{19}F NMR (376 MHz, acetone-d_6): δ -62.2 (s, 3F). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{14}H_{14}F_3NO_4B$, 328.0968; found, 328.0970.

Synthesis of α-Branched Allylic Sulfinamides

General procedures for the addition of alkenyl trifluoroborates to *N-tert*-butanesulfinyl imines (Procedures D and E).

Procedure D- glovebox procedure: Reactions were set up in a glovebox. Hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (2.9 mg, 0.0063 mmol, 0.025 equiv) was dissolved in DMF (0.2 mL, 1.25 M or 0.4 mL, 0.62 M) and added to a vial containing 1,2-bis(diphenylphosphino)benzene (5.6 mg, 0.013 mmol, 0.050 equiv). The resulting mixture of catalyst and ligand was added to a vial containing a stir-vane and the appropriate potassium alkenyltrifluoroborate (0.300-0.500 mmol, 1.2-2.0 equiv). To the mixture of catalyst, ligand, and trifluoroborate was added the appropriate sulfinyl imine (0.250 mmol, 1.0 equiv) dissolved in DMF (0.2 mL, 1.25 M or 0.4 mL, 0.62 M), followed by water (0.6 mL, 0.42 M or 1.2 mL, 0.21 M), and triethylamine (0.070 mL, 0.50 mmol, 2.0 equiv). The reaction vial was capped, removed from the glovebox, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C (aluminum block temperature) and stirred for 1-20 h. Upon heating and stirring, the reaction mixture becomes biphasic with globules of starting imine/product in the reaction medium. The reaction mixture was allowed to cool to rt and diluted with 20% EtOAc in hexanes (10 mL). The organic layer was washed with water (5 mL) to remove the DMF and the aqueous layer was extracted with 20% EtOAc in hexanes (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc:hexanes mixtures and were visualized with PMA stain.

Procedure E- Schlenk-line procedure: Reactions were set up in a fumehood using Schlenk technique. DMF, water, triethylamine, and the appropriate sulfinyl imine were added to separate round-bottom flasks and degassed by subjecting the liquids to vacuum for ~1 min and refilling with nitrogen gas (3x). DMF (0.62 M or 0.31 M) was added by cannula to a round-bottom flask containing hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (0.01-0.025 equiv) and 1,2-bis(diphenylphosphino)benzene (0.02-0.050 equiv). The catalyst and ligand were stirred under N_2 atmosphere until the solution was homogenous and then added by cannula to a round-bottom flask containing the appropriate potassium alkenyltrifluoroborate (2.0 equiv). The mixture of catalyst, ligand, and trifluoroborate was stirred under N_2 atmosphere until the solution was homogenous and added by cannula to a round-bottom flask containing the appropriate sulfinyl imine (1.0 equiv). To this mixture was added by cannula the water (0.42 M or 0.21 M) and by gas-tight syringe the triethylamine (2.0 equiv). The reaction mixture was placed in an oil-bath, heated to 60 °C, and stirred for 20 h. Upon heating and stirring, the reaction mixture becomes biphasic with globules of starting imine/product in the reaction medium. The reaction mixture was allowed to cool to rt and diluted with 20% EtOAc in hexanes. The organic layer was washed with water to remove the DMF and the aqueous layer was extracted with 20% EtOAc in hexanes (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc:hexanes mixtures and were visualized with PMA stain.

General procedures for the addition of MIDA boronates to *N-tert*-butanesulfinyl imines (Procedure F and G).

Procedure F- glovebox procedure: Reactions were set up in a glovebox. Hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (2.9 mg, 0.0063 mmol, 0.025 equiv) was dissolved in dioxane (0.4 mL, 0.62 M), and the resulting solution was added to a vial containing 1,2-bis(diphenylphosphino)benzene (5.6 mg, 0.013 mmol, 0.050 equiv). The mixture of catalyst and ligand was then added to a vial containing a stir-vane and the appropriate MIDA boronate (0.300-0.500 mmol, 1.2-2.0 equiv). To the mixture of catalyst, ligand, and MIDA boronate was added the appropriate sulfinyl imine (0.250 mmol, 1.0 equiv) dissolved in dioxane (0.4 mL, 0.62 M), followed by water (1.2 mL, 0.21 M), and K_3PO_4 (106 mg, 0.500 mmol, 2.0 equiv). The reaction vial was capped, removed from the inert atmosphere box, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C and stirred for 20 h. Upon heating and stirring, the reaction mixture becomes biphasic with globules of starting imine/product in the reaction medium. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL), and the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc/hexanes mixtures and were visualized with PMA stain.

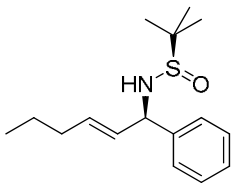
Procedure G- Schlenk-line procedure: Reactions were set up in a fumehood using Schlenk technique. The appropriate sulfinyl imine (0.250 mmol, 1.0 equiv) was added to a 2 mL single neck pear-shaped flask fitted with a rubber septum, which was subjected to three cycles of evacuation and refilling with nitrogen gas via an inlet needle. Water (1.2 mL) and K_3PO_4 (106 mg, 0.500 mmol, 2.0 equiv) were added to a separate 5 mL single neck round-bottom flask fitted with a rubber septum, which was subjected to three cycles of evacuation and refilling with

nitrogen gas via an inlet needle. A 5-mL Schlenk tube equipped with a vacuum adaptor, septum and stir bar, was charged with hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (2.9 mg, 0.0063 mmol, 0.025 equiv) and 1,2-bis(diphenylphosphino)benzene (5.6 mg, 0.013 mmol, 0.050 equiv). After evacuating and refilling the flask with N_2 gas (3x), freshly distilled dioxane (0.3 mL) was added by gas-tight syringe. The catalyst and ligand were stirred under N_2 atmosphere for 2 min, and then the septum was removed and the MIDA boronate (0.500 mmol, 2.0 equiv) was added while maintaining a strong N_2 gas flow. The mixture of catalyst, ligand, and MIDA boronate was stirred under a N_2 atmosphere until the solution was homogenous. Then the sulfinyl imine dissolved in dioxane (0.5 mL) followed by the aqueous K_3PO_4 solution were added by cannula. The Schlenk tube was capped, and the reaction mixture was heating in a 60 °C oil bath with stirring for 20 h whereupon the reaction mixture becomes biphasic with globules of starting imine/product in the reaction medium. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL), and the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc/hexanes mixtures and were visualized with PMA stain.

General procedure for the addition of alkenyl trifluoroborates to *N*-*tert*-butanesulfinyl ether imines (Procedure H). Reactions were set up in an inert atmosphere box. $[Rh(cod)(MeCN)_2]BF_4$ (0.050 equiv) was dissolved in DMF (0.25 M) and added to a vial containing 1,2-bis(diphenylphosphino)benzene (0.050 equiv). The resulting mixture of catalyst and ligand was added to a vial containing a stir-vane and the appropriate potassium alkenyltrifluoroborate (2.0 equiv). To the mixture of catalyst, ligand, and trifluoroborate was added the appropriate sulfinyl imine (1.0 equiv) dissolved in DMF (0.25 M), followed by water (9 equiv). The reaction vial was capped, removed from the inert atmosphere box, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C (aluminum block temperature) and stirred for 20 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL) and the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The products were isolated by silica gel chromatography using EtOAc:hexanes mixtures and were visualized with PMA stain.

General procedure for preparing authentic mixture of *N*-sulfinyl allylic amine diastereomers for diastereoselectivity determination. The authentic mixture of diastereomers were prepared according to literature procedure[25]: The *N*-sulfinyl amine (1.0 equiv) dissolved in CH_2Cl_2 (0.16 M) in an oven-dried vial equipped with a Teflon coated stir bar under nitrogen was placed in an ambient water bath. 4 M HCl in dioxane (2.2 equiv) was added dropwise to this solution, and the reaction mixture was stirred at rt for 0.5-1 h. NEt_3 (2.4 equiv) was then added dropwise and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc and washed successively with 1 N $NaHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide an authentic mixture of *N*-sulfinyl amine diastereomers. The extractive isolation provided analytically pure material. Separation conditions for the mixture of authentic diastereomers were then established by HPLC in hexanes/EtOH or hexanes/iPrOH. The dr was

determined for the crude products and was confirmed by coinjections with the authentic mixture of diastereomers.



(R_S)-*N*-((*R*,*E*)-1-(phenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3a).

- Procedure D was followed using sulfinyl imine **3.2a** (52.3 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 57.4 mg (82% yield, 99:1 dr) of **3.3a** as a pale yellow oil. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 16.7 min, t_{major} = 20.2 min. IR 3188, 2957, 1454, 1362, 1058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.4), 1.24 (s, 9H), 1.41 (sextet, 2H, *J* = 7.3), 2.03 (app q, 2H, *J* = 7.0), 3.46 (s, 1H), 4.93 (d, 1H, *J* = 8.1), 5.50 (dd, 1H, *J* = 8.1, 15.3), 5.79 (dt, 1H, *J* = 15.3, 6.9), 7.25-7.31 (m, 1H), 7.32-7.37 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.3, 22.9, 34.5, 55.6, 61.1, 127.2, 128.0, 129.0, 130.3, 134.5, 142.6. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{16}H_{26}NOS$, 280.1735; found, 280.1730.

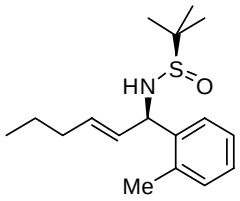
- Procedure D was followed using sulfinyl imine **3.2a** (52.3 mg, 0.250 mmol) and trifluoroborate **3.1a** (52.8 mg, 0.300 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 52.5 mg (75% yield, 99:1 dr) of **3.3a** as a pale yellow oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.

- Procedure E was followed using sulfinyl imine **3.2a** (52.3 mg, 0.250 mmol), trifluoroborate **3.1a** (0.088 g, 0.50 mmol), hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (2.9 mg, 0.0063 mmol), 1,2-bis(diphenylphosphino)benzene (5.6 mg, 0.013 mmol), and triethylamine (0.070 mL, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 57.6 mg (82% yield, 99:1 dr) of **3.3a** as a yellow oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.

- Procedure F was followed using sulfinyl imine **3.2a** (52.3 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 68.4 mg (98% yield, 99:1 dr) of **3.3a** as a colorless oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.

- Procedure F was followed using sulfinyl imine **3.2a** (52.3 mg, 0.250 mmol) and MIDA boronate **3.4a** (67.5 mg, 0.300 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 67.0 mg (96% yield, 99:1 dr) of **3.3a** as a colorless oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.

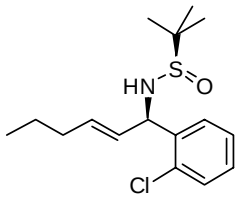
- Procedure G was followed using sulfinyl imine **3.2a** (52.3 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 64.2 mg (92% yield, 99:1 dr) of **3.3a** as a colorless oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*R*,*E*)-1-(2-methylphenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3b).

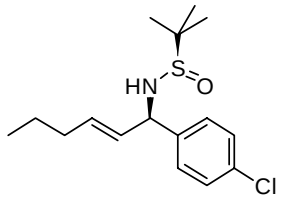
– Procedure D was followed using sulfinyl imine **3.2b** (55.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-70% EtOAc/hexanes) afforded 60.9 mg (83% yield, >99:1 dr) of **3.3b** as a clear oil. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 25.3 min, t_{major} = 27.7 min. IR 3198, 2957, 1463, 1363, 1062 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.4), 1.25 (s, 9H), 1.40 (sextet, 2H, *J* = 7.3), 2.02 (app qd, 2H, *J* = 7.0, 1.3), 2.37 (s, 3H), 3.39 (d, 1H, *J* = 1.3), 5.14 (dd, 1H, *J* = 8.1, 1.8), 5.42 (ddt, 1H, *J* = 8.1, 15.2, 1.3), 5.77 (dt, 1H, *J* = 15.2, 6.8), 7.12-7.25 (m, 3H), 7.38-7.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.5, 22.4, 22.9, 34.5, 55.6, 56.8, 126.3, 126.6, 127.6, 129.5, 131.0, 134.7, 135.8, 140.3. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{17}H_{28}NOS$, 294.1892; found, 294.1887.

- Procedure F was followed using sulfinyl imine **3.2b** (55.8 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 72.7 mg (99% yield, >99:1 dr) of **3.3b** as a colorless oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*R*,*E*)-1-(2-chlorophenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3c). Procedure D was followed using sulfinyl imine **3.2c** (15.2 mg, 0.0625 mmol), trifluoroborate **3.1a** (22.0 mg, 0.125 mmol), hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (0.7 mg, 0.0016 mmol), 1,2-bis(diphenylphosphino)benzene (1.4 mg, 0.0031 mmol), and triethylamine (0.017 mL, 0.125 mmol) in 2:3 DMF:H_2O (0.2:0.3 mL). The reaction mixture was stirred for 20 h and the yield (78%) was determined by ^{1}H-NMR relative to an external standard. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 7.5), 1.23 (s, 9H), 1.38 (sextet, 2H, *J* = 7.5), 2.01 (app q, 2H, *J*

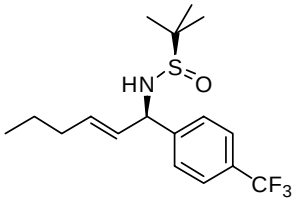
= 7.0), 3.56 (d, 1H, *J* = 3.0), 5.37 (dd, 1H, *J* = 3.0, 7.5), 5.43 (dd, 1H, *J* = 7.5, 15.0), 5.79 (dt, 1H, *J* = 15.0, 6.5), 7.19 (td, 1H, *J* = 7.5, 1.5), 7.26 (td, 1H, *J* = 7.8, 1.1), 7.34 (dd, 1H, *J* = 7.8, 1.1), 7.45 (dd, 1H, *J* = 7.5, 1.5).



(R_S)-*N*-((*R*,*E*)-1-(4-chlorophenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3d).

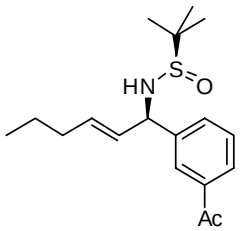
- Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 10-80% EtOAc/hexanes) afforded 73.4 mg (94% yield, 99:1 dr) of **3.3d** as a clear oil. HPLC (silica column, hexanes:*i*PrOH 99:1, 1.0 mL/min, λ = 222 nm): t_{minor} = 66.0 min, t_{major} = 69.0 min. IR 3194, 2956, 1490, 1363, 1056 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.4), 1.24 (s, 9H), 1.40 (sextet, 2H, *J* = 7.3), 2.03 (app q, 2H, *J* = 7.0), 3.41 (s, 1H), 4.90 (dd, 1H, *J* = 7.9, 2.0), 5.46 (dd, 1H, *J* = 7.9, 15.3), 5.77 (dt, 1H, *J* = 15.3, 6.9), 7.28 (d, 2H, *J* = 8.4), 7.31 (d, 2H, *J* = 8.4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.2, 22.9, 34.4, 55.7, 60.6, 128.6, 129.1, 129.9, 133.7, 134.9, 141.0. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{16}H_{25}NOSCl$, 314.1345; found, 314.1351.

- Procedure F was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 76.6 mg (98% yield, 99:1 dr) of **3.3d** as a colorless oil. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 30.3 min, t_{major} = 31.5 min. ^1H NMR data corresponded to data reported above for Procedure D.

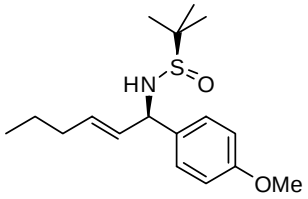


(R_S)-*N*-((*R*,*E*)-1-(4-(trifluoromethyl)phenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3e). Procedure D was followed using sulfinyl imine **3.2e** (69.3 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 10-80% EtOAc/hexanes) afforded 83.8 mg (96% yield, 98:2 dr) of **3.3e** as a clear oil. HPLC (silica column, hexanes:EtOH 99:1, 1.0 mL/min, λ = 222 nm): t_{minor} = 30.2 min, t_{major} = 32.0 min. IR 2962, 1323, 1165, 1122, 1067, 1018 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.5), 1.25 (s, 9H), 1.41 (sextet, 2H, *J* = 7.5), 2.04 (app q, 2H, *J* = 7.0), 3.50 (s, 1H), 4.99 (d, 1H, *J* =

8.0), 5.48 (dd, 1H, J = 8.8, 15.0), 5.81 (dt, 1H, J = 15.0, 7.0), 7.48 (d, 2H, J = 8.0), 7.61 (d, 2H, J = 8.0). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.2, 22.8, 34.4, 55.8, 60.9, 127.6, 124.2 (q, J = 271.2), 125.9 (q, J = 3.8), 129.6, 130.1 (q, J = 31.2), 135.4, 146.4. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{17}H_{25}NOF_3S$, 348.1609; found, 348.1608.



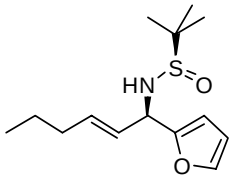
(R_S)-*N*-((*R*,*E*)-1-(3-acetylphenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3f). Procedure D was followed using sulfinyl imine **3.2f** (62.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 30-80% EtOAc/hexanes) afforded 77.5 mg (96% yield, 99:1 dr) of **3.3f** as a clear oil. HPLC (silica column, hexanes:EtOH 95:5, 1.0 mL/min, λ = 222 nm): t_{minor} = 10.6 min, t_{major} = 13.8 min. IR 3229, 2958, 1683, 1360, 1271, 1122, 1055 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, J = 7.4), 1.23 (s, 9H), 1.39 (sextet, 2H, J = 7.3), 2.02 (app qd, 2H, J = 7.1, 1.3), 2.58 (s, 3H), 3.46 (d, 1H J = 2.5), 4.96 (dd, 1H, J = 7.8, 2.5), 5.50 (ddt, 1H, J = 7.8, 15.2, 1.3), 5.78 (dt, 1H, J = 15.2, 7.1), 7.43 (t, 1H, J = 7.8), 7.54 (dt, 1H, J = 7.8, 1.3), 7.84 (dt, 1H, J = 7.8, 1.3), 7.92 (t, 1H, J = 1.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.2, 22.8, 26.9, 34.4, 55.8, 61.1, 127.0, 128.0, 129.3, 129.9, 132.0, 135.1, 137.8, 143.2, 198.0. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{18}H_{28}NOS$, 322.1841; found, 322.1832.



(R_S)-*N*-((*R*,*E*)-1-(4-methoxyphenyl)hex-2-enyl)-2-methylpropanesulfinamide (3.3g).

- Procedure D was followed using sulfinyl imine **3.2g** (59.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 40.5 mg (52% yield, 99:1 dr) of **3.3g** as a clear oil. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 15.8 min, t_{major} = 21.2 min. IR 3223, 2957, 1610, 1511, 1463, 1246, 1059, 1036 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.4), 1.24 (s, 9H), 1.40 (sextet, 2H, J = 7.5), 2.02 (app q, 2H, J = 7.0), 3.39 (d, 1H, J = 1.5), 3.79 (s, 3H), 4.88 (dd, 1H, J = 8.2, 1.5), 5.49 (dd, 1H, J = 8.1, 15.3), 5.75 (dt, 1H, J = 15.3, 6.7), 6.87 (d, 2H, J = 8.7), 7.27 (d, 2H, J = 8.7). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.3, 22.9, 34.5, 55.4, 55.5, 60.5, 114.3, 128.4, 130.5, 134.1, 134.7, 159.3. HRMS-ESI (m/z): $[MNa]^+$ calcd for $C_{17}H_{27}NO_2SNa$, 332.1655; found, 332.1661.

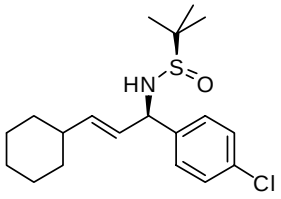
- Procedure F was followed using sulfinyl imine **3.2g** (59.8 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 65.6 mg (85% yield, 99:1 dr) of **3.3g** as a colorless oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*R*,*E*)-1-(furan-2-yl)hex-2-enyl)-2-methylpropanesulfinamide (3.3h).

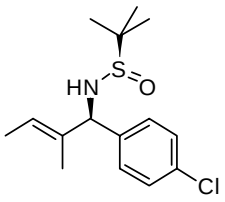
- Procedure D was followed using sulfinyl imine **3.2h** (49.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 25.1 mg (37% yield, 98:2 dr) of **3.3h** as a pale yellow oil. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 16.1 min, t_{major} = 21.1 min). IR 3196, 2958, 1459, 1363, 1060, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.4), 1.20 (s, 9H), 1.41 (sextet, 2H, J = 7.4), 2.05 (app q, 2H, J = 6.9), 3.56 (d, 1H, J = 3.4), 4.95 (dd, 1H, J = 3.4, 7.7), 5.53 (ddt, 1H, J = 7.7, 15.3, 1.4), 5.77 (dt, 1H, J = 15.3, 6.7), 6.20 (d, 1H, J = 3.2), 6.30 (dd, 1H, J = 3.2, 1.8), 7.36 (d, 1H, J = 1.8). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.8, 22.2, 22.7, 34.4, 55.1, 55.8, 106.9, 110.4, 127.3, 135.7, 142.4, 154.4. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{14}H_{24}NO_2S$, 270.1526; found, 270.1522.

- Procedure F was followed using sulfinyl imine **3.2h** (49.8 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 47.5 mg (71% yield, 98:2 dr) of **3.3h** as a pale yellow oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.

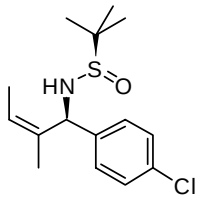


(R_S)-*N*-((*R*,*E*)-1-(4-chlorophenyl)-3-cyclohexylallyl)-2-methylpropanesulfinamide (3.3i). Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1b** (108 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 80.4 mg (91% yield, 99:1 dr) of **3.3i** as a pale yellow oil, which solidified upon cooling. R_f = 0.27 (50% EtOAc/hexanes). mp 66.8-67.4 ºC. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm): t_{minor} = 9.6 min, t_{major} = 11.0 min. IR 3099, 2922, 1488, 1049 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00-1.31 (m, 5H), 1.23 (s, 9H), 1.59-1.76 (m, 5H), 1.94-2.03 (m, 1H), 3.40 (d, 1H, J

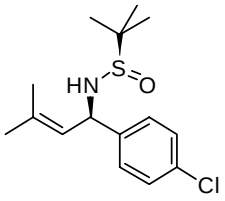
= 1.8), 4.88 (dd, 1H, *J* = 7.9, 2.1), 5.41 (dd, 1H, *J* = 7.9, 15.4), 5.73 (dd, 1H, *J* = 15.4, 6.6), 7.25-7.33 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.9, 26.0, 26.1, 26.2, 32.7, 32.8, 40.5, 55.7, 60.6, 127.3, 128.6, 129.1, 133.6, 140.7, 141.1. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{19}H_{29}NOSCl$, 354.1658; found, 354.1655.



(R_S)-*N*-((*R*,*E*)-1-(4-chlorophenyl)-2-methylbut-2-enyl)-2-methylpropanesulfinamide (3.3j). Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1c** (81 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 72.9 mg (97% yield, 96:4 dr) of **3.3j** as a pale yellow oil. R_f = 0.22 (50% EtOAc/hexanes). HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{major} = 13.4 min, t_{minor} = 16.9 min. IR 3272, 2958, 2920, 1490, 1033, 1011 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.45 (s, 3H), 1.66 (d, 3H, *J* = 6.7), 3.41 (s, 1H), 4.93 (d, 1H, *J* = 1.7), 5.82 (q, 1H, *J* = 6.7), 7.27 (d, 2H, *J* = 8.7), 7.30 (d, 2H, *J* = 8.7). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7, 13.6, 22.9, 55.6, 65.1, 125.0, 128.4, 128.8, 133.5, 134.0, 140.0. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{15}H_{23}NOSCl$, 300.1189; found, 300.1189.



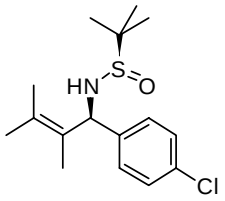
(R_S)-*N*-((*R*,*Z*)-1-(4-chlorophenyl)-2-methylbut-2-enyl)-2-methylpropanesulfinamide (3.3l). Procedure D was followed using sulfinyl imine **3.2d** (15.2 mg, 0.0625 mmol), trifluoroborate **3.1e** (20.3 mg, 0.125 mmol), hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (0.7 mg, 0.0016 mmol), 1,2-bis(diphenylphosphino)benzene (1.4 mg, 0.0031 mmol), and triethylamine (0.017 mL, 0.125 mmol) in 2:3 DMF:H_2O (0.2:0.3 mL). The reaction mixture was stirred for 20 h, and the yield (87%) and isomer ratio (91:9 *Z*/*E*) were determined by ^{1}H-NMR relative to an external standard. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 9H), 1.51 (s, 3H), 1.77 (d, 3H, *J* = 6.5), 3.48 (s, 1H), 5.55 (d, 1H, *J* = 2.5), 5.58 (q, 1H, *J* = 6.5), 7.28 (d, 2H, *J* = 9.0), 7.32 (d, 2H, *J* = 9.0). (ESI): *m/z* 300 $[MH]^+$.



(R_S)-*N*-((*R*)-1-(4-chlorophenyl)-3-methylbut-2-enyl)-2-methylpropanesulfinamide (3.3k).

- Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **1.4d** (81 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 52.1 mg (70% yield, 98:2 dr) of **3.3k** as a pale yellow oil. R_f = 0.29 (50% EtOAc/hexanes). HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{major} = 12.8 min, t_{minor} = 15.1 min. IR 3227, 2916, 1491, 1048, 1010 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.75 (s, 3H), 1.80 (s, 3H), 3.44 (s, 1H), 5.15-5.22 (m, 2H), 7.28 (d, 2H, *J* = 9.0), 7.31 (d, 2H, *J* = 9.0). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.6, 22.9, 26.2, 55.6, 55.8, 124.8, 128.5, 129.1, 133.5, 136.7, 141.4. MS (ESI): *m/z* 300 $[MH]^+$. Anal. Calcd for $C_{15}H_{22}NOSCl$: C, 60.08; H, 7.40; N, 4.67. Found: C, 60.11; H, 7.49; N, 4.68.

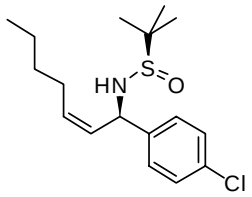
- Procedure F was followed using sulfinyl imine **3.2d (**60.9 mg, 0.250 mmol) and MIDA boronate **3.4d** (106 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 69.6 mg (93% yield, 98:2 dr) of **3.3k** as a colorless oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.



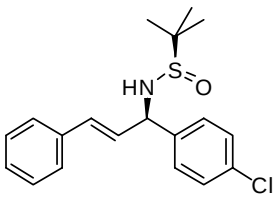
(R_S)-*N*-((*S*)-1-(4-chlorophenyl)-2,3-dimethylbut-2-enyl)-2-methylpropanesulfinamide (3.3m).

- Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1f** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 58.3 mg (75% yield, 99:1 dr) of **3.3m** as a white solid. R_f = 0.36 (50% EtOAc/hexanes). Crystallization from EtOH/H_2O yielded x-ray quality crystals. mp 80.8-81.6 ºC. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 13.0 min, t_{major} = 14.7 min. IR 3225, 2920, 1486, 1058, 1009 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.28 (s, 9H), 1.42 (s, 3H), 1.73 (s, 3H), 1.99 (s, 3H), 3.49 (s, 1H), 5.59 (d, 1H, *J* = 2.4), 7.25 (d, 2H, *J* = 8.5), 7.29 (d, 2H, *J* = 8.5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 20.8, 21.6, 22.9, 55.5, 57.6, 125.4, 128.1, 128.7, 131.7, 133.1, 140.6. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{16}H_{25}NOSCl$, 314.1345; found, 314.1346.

- Procedure F was followed using sulfinyl imine **3.2d** (29.3 mg, 0.250 mmol), MIDA boronate **3.4f** (54.0 mg, 0.500 mmol), $[Rh(OH)(cod)]_2$ (1.4 mg, 0.0030 mmol), dppbenz (2.7 mg, 0.006 mmol), and K_3PO_4 (50.9 mg, 0.240 mmol) in 2:3 dioxane:H_2O (0.4:.6 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 31.9 mg (85% yield, 99.5:0.5 dr) of **3.3m** as a pale yellow oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*R*,*Z*)-1-(4-chlorophenyl)hept-2-enyl)-2-methylpropanesulfinamide (3.3n). Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1g** (95 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 80 min. The short reaction time was important for preventing isomerization of the product. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 74.5 mg (91% yield, 99:1 Z/E, 98:2 dr) of **3.3n** as a clear oil. R_f = 0.48 (50% EtOAc/hexanes). HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 20.3 min, t_{major} = 24.3 min. IR 3191, 2956, 2927, 1490, 1056, 1013 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.0), 1.23 (s, 9H), 1.27-1.45 (m, 4H), 2.12-2.30 (m, 2H), 3.42 (s, 1H), 5.26 (d, 1H, *J* = 9.0), 5.43 (t, 1H, *J* = 9.0), 5.58-5.66 (m, 1H), 7.27-7.33 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 22.6, 22.8, 27.7, 31.8, 54.8, 55.7, 128.6, 129.2, 129.3, 133.7, 134.1, 141.1. MS (ESI): *m/z* 328 $[MH]^+$. Anal. Calcd for $C_{17}H_{26}NOSCl$: C, 62.27; H, 7.99; N, 4.27. Found: C, 62.48; H, 8.18; N, 4.18.

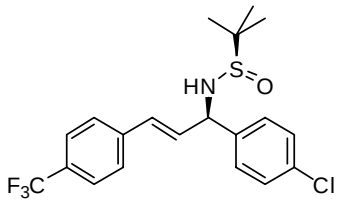


(R_S)-*N*-((*R*,*E*)-1-(4-chlorophenyl)-3-phenylallyl)-2-methylpropanesulfinamide (3.3o).

- Procedure C was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1h** (105 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 57.4 mg (66% yield, 99:1 dr) of **3.3o** as a clear oil. R_f = 0.27 (50% EtOAc/hexanes). mp 111.6-112.6 ºC. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 254 nm): t_{minor} = 12.7 min, t_{major} = 14.3 min. IR 2863, 1491, 1060, 982 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 9H), 3.54 (d, 1H, *J* = 2.3), 5.12 (dd, 1H, *J* = 7.9, 2.3), 6.19 (dd, 1H, *J* = 8.0, 15.8), 6.68 (d, 1H, *J* = 15.8), 7.21-7.40 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.9, 55.9, 60.7, 126.8, 128.2, 128.7, 128.8, 129.2, 129.3, 133.0, 134.0, 136.3, 140.3. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{19}H_{23}NOSCl$, 348.1189; found, 348.1193.

- Procedure F was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and commercially available (*E*)-styryl MIDA boronate **3.4h** (130 mg, 0.500 mmol) in 2:3

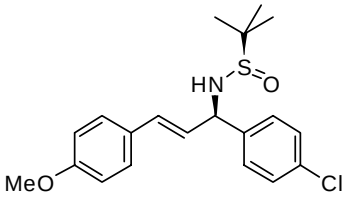
dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 79.0 mg (91% yield, 99:1 dr) of **3.3o** as a pale yellow oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*R*,*E*)-1-(4-chlorophenyl)-3-(4-(trifluoro)phenyl)allyl)-2-methylpropanesulfinamide (3.3p).

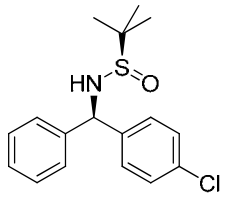
- Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1i** (140 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 22.8 mg (22% yield, 99:1 dr) of **3.3p** as a pale yellow oil. R_f = 0.21 (50% EtOAc/hexanes). HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 254 nm): t_{minor} = 12.8 min, t_{major} = 18.0 min. IR 3189, 2957, 1323, 1163, 1122, 1065 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 3.57 (d, 1H, *J* = 2.3), 5.14 (dd, 1H, *J* = 7.9, 2.3), 6.29 (dd, 1H, *J* = 7.9, 15.8), 6.72 (d, 1H, *J* = 15.8), 7.35 (s, 4H), 7.46 (d, 2H, *J* = 8.3), 7.56 (d, 2H, *J* = 8.3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 56.1, 60.5, 124.3 (q, *J* = 272.2), 125.8 (q, *J* = 3.7), 127.0, 128.8, 129.5, 130.0 (q, *J* = 32.3), 131.7, 131.9, 134.4, 139.78, 139.81. ^{19}F NMR (376 MHz, acetone-d_6): δ -61.8 (s). HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{20}H_{22}NOF_3SCl$, 416.1063; found, 416.1060.

- Procedure F was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and MIDA boronate **3.4i** (164 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 10-80% EtOAc/CH_2Cl_2) afforded 14.5 mg (14% yield, 99:1 dr) of **3.3p** as a pale yellow oil. ^{1}H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*R*,*E*)-1-(4-chlorophenyl)-3-(4-methoxyphenyl)allyl)-2-methylpropanesulfinamide (3.3r). Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and trifluoroborate **3.1k** (120 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 85.6 mg (91% yield, 99:1 dr) of **3.3r** as a yellow solid. R_f = 0.20 (50% EtOAc/hexanes). mp 121.4-122.7 ºC. HPLC (silica column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 254 nm): t_{minor} = 22.4 min, t_{major} = 24.0 min. IR 2926, 1511, 1253, 1174, 1059, 1027 cm^{-1}. ^{1}H

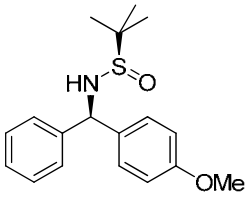
NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 9H), 3.56 (d, 1H, *J* = 2.0), 3.78 (s, 3H), 5.09 (dd, 1H, *J* = 8.1, 2.0), 6.04 (dd, 1H, *J* = 8.1, 15.7), 6.62 (d, 1H, *J* = 15.7), 6.83 (d, 2H, *J* = 8.6), 7.28-7.37 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 55.4, 55.8, 60.8, 114.1, 126.9, 128.0, 128.7, 129.1, 129.2, 132.6, 133.9, 140.6, 159.7. MS (ESI): *m/z* 400 $[MNa]^+$. Anal. Calcd for $C_{20}H_{24}NO_2SCl$: C, 63.56; H, 6.40; N, 3.71. Found: C, 63.79; H, 6.66; N, 4.04.



(R_S)-*N*-((*R*)-1-(4-chlorophenyl)-1-phenylmethyl)-2-methylpropanesulfinamide (3.6a).

- Procedure D was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and commercially available trifluoroborate **3.1l** (92 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 67.5 mg (84% yield, 96:4 dr) of **3.6a** as a pale yellow solid. HPLC (silica column, hexanes:*i*PrOH 99:1, 1.0 mL/min, λ = 222 nm): t_{major} = 24.3 min, t_{minor} = 31.9 min). ^1H NMR data corresponded to previously reported data for the enantiomer.[3d]

- Procedure F was followed using sulfinyl imine **3.2d** (60.9 mg, 0.250 mmol) and commercially available MIDA boronate **3.4l** (117 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 78.1 mg (97% yield, 98:2 dr) of **3.6a** as a pale yellow solid. HPLC (silica column, hexanes:*i*PrOH 99:1, 1.0 mL/min, λ = 222 nm): t_{major} = 24.2 min, t_{minor} = 31.8 min. ^1H NMR corresponded to previously reported data for the enantiomer.[3d]

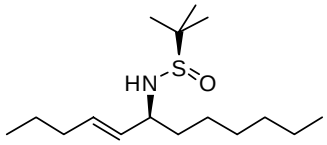


(R_S)-*N*-((*R*)-1-(4-methoxyphenyl)-1-phenylmethyl)-2-methylpropanesulfinamide (3.6b).

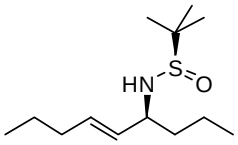
- Procedure D was followed using sulfinyl imine **3.2g** (59.8 mg, 0.250 mmol) and commercially available trifluoroborate **3.1l** (92 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 40.0 mg (50% yield, 94:6 dr) of **3.6b** as a colorless oil. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 20.4 min, t_{major} = 22.1 min). ^1H NMR data corresponded to previously reported data for the enantiomer.[3d]

- Procedure F was followed using sulfinyl imine **3.2g** (59.8 mg, 0.250 mmol) and commercially available MIDA boronate **3.4l** (117 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+

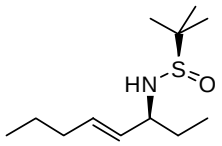
cartridge, 12-100% EtOAc/hexanes) afforded 70.6 mg (89% yield, 98:2 dr) of **3.6b** as a colorless oil. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 20.4 min, t_{major} = 22.0 min. ^{1}H NMR data corresponded to previously reported data for the enantiomer.[3d]



(*R*$_S$)-*N*-((*S*,*E*)-dodec-4-en-6-yl)-2-methylpropanesulfinamide (3.7a). Procedure D was followed using sulfinyl imine **3.2i** (54.3 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.4:0.6 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 51.8 mg (72% yield, 98:2 dr) of **3.7a** as a pale yellow oil. R_f = 0.39 (50% EtOAc/hexanes). HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 21.6 min, t_{major} = 24.6 min. IR 3198, 2956, 2926, 1457, 1363, 1054, 967 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, 3H, *J* = 7.0), 0.86 (t, 3H, *J* = 7.3), 1.16 (s, 9H), 1.18-1.31 (m, 8H), 1.37 (sextet, 2H, *J* = 7.3), 1.41-1.56 (m, 2H), 1.98 (app q, 2H, *J* = 7.0), 3.05 (s, 1H), 3.66-3.73 (m, 1H), 5.16 (dd, 1H, *J* = 7.9, 15.3), 5.58 (dt, 1H, *J* = 15.3, 7.0). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 14.2, 22.4, 22.7, 22.8, 25.8, 29.2, 31.8, 34.4, 37.0, 55.3, 57.7, 131.1, 133.9. HRMS-ESI (m/z): [MH]$^+$ calcd for $C_{16}H_{34}NOS$, 288.2356; found, 288.2354.

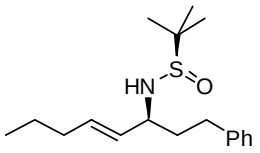


(*R*$_S$)-*N*-((*S*,*E*)-non-5-en-4-yl)-2-methylpropanesulfinamide (3.7b). Procedure D was followed using sulfinyl imine **3.2j** (43.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.4:0.6 mL). The reaction mixture was stirred for 14 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 38.0 mg (62% yield, 98:2 dr) of **3.7b** as a pale yellow oil. HPLC (silica column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 12.7 min, t_{major} = 15.9 min. IR 3205, 2957, 2927, 1457, 1362, 1053, 967 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.0), 0.89 (t, 3H, *J* = 7.0), 1.17 (s, 9H), 1.25-1.54 (m, 6H), 1.99 (app q, 2H, *J* = 7.0), 3.06 (d, 1H, *J* = 2.5), 3.69-3.77 (m, 1H), 5.17 (ddt, 1H, *J* = 8.2, 15.3, 1.3), 5.60 (dt, 1H, *J* = 15.3, 6.7). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 14.1, 19.1, 22.5, 22.7, 34.5, 39.1, 55.3, 57.5, 131.0, 133.9. HRMS-ESI (m/z): [MH]$^+$ calcd for $C_{13}H_{28}NOS$, 246.1886; found, 246.1885.



(*R*$_S$)-*N*-((*S*,*E*)-oct-4-en-3-yl)-2-methylpropanesulfinamide (3.7c). Procedure D was followed using sulfinyl imine **3.2k** (40.3 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.4:0.6 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 30.3 mg (52% yield, 98:2 dr) of **3.7c**

as a clear oil. There seems to be a correlation between the efficiency of the alkenylation reaction and the hydrophobicity of the imine substrates. The increased solubility of imine **3.2k** in DMF/H_2O could be resulting in increased imine hydrolysis and hence a slightly reduced yield. HPLC (silica column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 12.1 min, t_{major} = 16.4 min. IR 3206, 2958, 2927, 1456, 1362, 1052, 966 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.3), 0.90 (t, 3H, *J* = 7.3), 1.19 (s, 9H), 1.40 (sextet, 2H, *J* = 7.3), 1.45-1.65 (m, 2H), 2.02 (app q, 2H, *J* = 6.8), 3.08 (d, 1H, *J* = 2.0), 3.62-3.70 (m, 1H), 5.18 (ddt, 1H, *J* = 8.1, 15.2, 1.3), 5.62 (dt, 1H, *J* = 15.2, 6.8). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.3, 13.8, 22.5, 22.8, 29.9, 34.5, 55.3, 59.1, 130.7, 134.2. MS (ESI): *m/z* 332 $[MH]^+$. Anal. Calcd for $C_{12}H_{25}NOS$: C, 62.29; H, 10.89; N, 6.05. Found: C, 62.65; H, 11.09; N, 5.69.

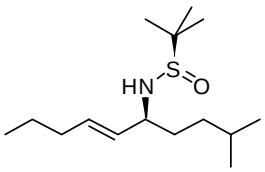


(R_S)-*N*-((*S*,*E*)-1-phenyloct-4-en-3-yl)-2-methylpropanesulfinamide (3.7d).

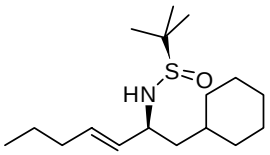
- Procedure D was followed using sulfinyl imine **3.2l** (47.5 mg, 0.200 mmol), trifluoroborate **3.1a** (70 mg, 0.40 mmol), hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (2.3 mg, 0.0050 mmol), 1,2-bis(diphenylphosphino)benzene (4.5 mg, 0.010 mmol), and triethylamine (0.056 mL, 0.40 mmol) in 2:3 DMF:H_2O (0.32:0.48 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 30-40% EtOAc/hexanes) afforded 47.7 mg (78% yield, 99:1 dr) of **3.7d** as a pale yellow oil which solidified upon storing at -20 ºC. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 13.0 min, t_{major} = 15.4 min. mp 37.1-37.9 ºC. IR 3200, 2953, 2921, 1454, 1052 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.5), 1.18 (s, 9H), 1.43 (sextet, 2H, *J* = 7.5), 1.79-1.95 (m, 2H), 2.07 (app q, 2H, *J* = 7.0), 2.56-2.65 (m, 1H), 2.66-2.73 (m, 1H), 3.13 (d, 1H, *J* = 1.3), 3.76-3.83 (m, 1H), 5.27 (ddt, 1H, *J* = 8.2, 15.4, 1.2), 5.67 (dt, 1H, *J* = 15.4, 6.8), 7.14-7.20 (m, 3H), 7.24-7.30 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.5, 22.7, 32.2, 34.5, 38.5, 55.4, 57.5, 126.1, 128.57, 128.61, 130.7, 134.6, 141.6. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{18}H_{30}NOS$, 308.2048; found, 308.2056.

- Procedure E (large scale reaction) was followed using sulfinyl imine **3.2l** (2.37 g, 10.0 mmol), trifluoroborate **3.1a** (3.52 g, 20.0 mmol), hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (45.6 mg, 0.100 mmol), 1,2-bis(diphenylphosphino)benzene (89.3 mg, 0.200 mmol), and triethylamine (2.79 mL, 20.0 mmol) in 2:3 DMF:H_2O (16:24 mL). Column chromatography (SiO_2, 10-60% EtOAc/hexanes) afforded 2.30 g (75% yield, 99:1 dr) of **3.7d** as a yellow oil which solidifed upon storing at -20 ºC to an off-white solid. Anal. Calcd for $C_{18}H_{29}NOS$: C, 70.31; H, 9.51; N, 4.56. Found: C, 70.39; H, 9.76; N, 4.62. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.

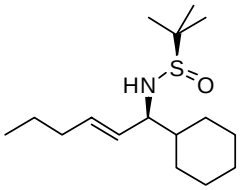
- Procedure F was followed using sulfinyl imine **3.2l** (59.4 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 60.5 mg (79% yield, 99:1 dr) of **3.7d** as a pale yellow oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.



(R_S)-*N*-((*S*,*E*)-2-methyldec-6-en-5-yl)-2-methylpropanesulfinamide (3.7e). Procedure D was followed using sulfinyl imine **3.2m** (50.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 14 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 52.2 mg (76% yield, 98:2 dr) of **3.7e** as a gel-like solid. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 22.6 min, t_{major} = 25.7 min. R_f = 0.44 (50% EtOAc/hexanes). IR 3202, 2955, 2925, 1465, 1364, 1054, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, 6H, *J* = 6.6), 0.87 (t, 3H, *J* = 7.3), 1.08-1.11 (m, 2H), 1.17 (s, 9H), 1.37 (sextet, 2H, *J* = 7.3), 1.43-1.58 (m, 3H), 1.99 (app q, 2H, *J* = 7.0), 3.05 (d, 1H, *J* = 2.3), 3.63-3.72 (m, 1H), 5.16 (dd, 1H, *J* = 8.3, 15.2), 5.58 (dt, 1H, *J* = 15.2, 7.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.5, 22.6, 22.8, 28.1, 34.5, 34.8, 35.0, 55.3, 58.0, 131.1, 134.0. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{15}H_{32}NOS$, 274.2199; found, 274.2200.



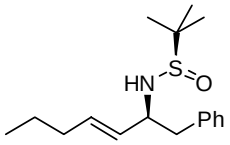
(R_S)-*N*-((*S*,*E*)-1-cyclohexylhept-3-en-2-yl)-2-methylpropanesulfinamide (3.7f). Procedure C was followed using sulfinyl imine **3.2n** (57.3 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 19 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 47.7 mg (64% yield, 98:2 dr) of **3.7f** as a white solid. mp 55.0-56.4 ºC. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 18.2 min, t_{major} = 20.9 min. R_f = 0.45 (50% EtOAc/hexanes). IR 3139, 2918, 2851, 1446, 1358, 1050, 968 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.81-0.98 (m, 3H), 0.89 (t, 3H, *J* = 7.3), 1.19 (s, 9H), 1.10-1.45 (m, 7H), 1.62-1.76 (m, 5H), 2.01 (app q, 2H, *J* = 7.1), 3.02 (d, 1H, *J* = 2.3), 3.81-3.90 (m, 1H), 5.17 (ddt, 1H, *J* = 8.6, 15.2, 1.3), 5.61 (dt, 1H, *J* = 15.2, 7.1). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.5, 22.8, 26.3, 26.4, 26.7, 33.1, 33.8, 34.3, 34.5, 44.6, 55.2, 55.3, 131.3, 133.8. MS (ESI): *m/z* 300 $[MH]^+$. Anal. Calcd for $C_{17}H_{33}NOS$: C, 68.17; H, 11.11; N, 4.68. Found: C, 68.42; H, 11.50; N, 4.35.



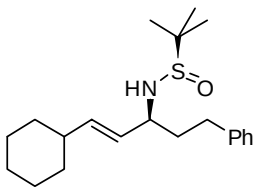
(R_S)-*N*-((*S*,*E*)-1-cyclohex-2-enyl)-2-methylpropanesulfinamide (3.7g).

- Procedure D was followed using sulfinyl imine **3.2o** (53.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (88 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 4 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 31.8 mg (45% yield, 98:2 dr) of **3.7g** as a clear oil. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 10.0 min, t_{major} = 13.8 min. IR 3199, 2922, 2852, 1450, 1362, 1055, 969 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.86-1.22 (m, 5H), 0.89 (t, 3H, *J* = 7.3), 1.19 (s, 9H), 1.34-1.47 (m, 3H), 1.61-1.78 (m, 5H), (app q, 2H, *J* = 7.2), 3.16 (s, 1H), 3.52-3.58 (m, 1H), 5.19 (dd, 1H, *J* = 8.8, 15.6), 5.58 (dt, 1H, *J* = 15.6, 6.6). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.6, 22.9, 26.4, 26.6, 28.6, 34.6, 43.7, 55.4, 62.4, 128.9, 134.9. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{16}H_{32}NOS$, 286.2199; found, 286.2193.

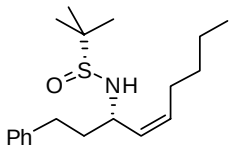
- Procedure F was followed using sulfinyl imine **3.2o** (53.9 mg, 0.250 mmol) and MIDA boronate **3.4a** (113 mg, 0.500 mmol) in 2:3 dioxane:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 14.9 mg (21% yield, 98:2 dr) of **3.7g** as a colorless oil. ^1H NMR and HPLC data corresponded to data reported above for Procedure D.



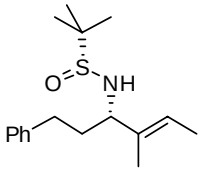
(R_S)-*N*-((*S*,*E*)-1-phenylhept-3-en-2-yl)-2-methylpropanesulfinamide (3.7j). Procedure D was followed using sulfinyl imine **3.2r** (55.8 mg, 0.250 mmol) and trifluoroborate **3.1a** (0.088 g, 0.50 mmol) in 2:3 DMF:H_2O (0.4:0.6 mL). The reaction mixture was stirred for 4 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 32.0 mg (44% yield, 97:3 dr) of **3.7j** as a yellow oil. HPLC (silica column, hexanes:*i*PrOH 97:3, 1.0 mL/min, λ = 222 nm): t_{minor} = 14.8 min, t_{major} = 19.1 min. IR 3199, 2956, 2926, 1454, 1362, 1052, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 7.3), 1.14 (s, 9H), 1.36 (sextet, 2H, *J* = 7.3), 2.00 (app q, 2H, *J* = 7.2), 2.79 (dd, 1H, *J* = 7.6, 13.3), 2.91 (dd, 1H, *J* = 6.0, 13.3), 3.23 (d, 1H, *J* = 2.0), 4.00-4.07 (m, 1H), 5.27 (dd, 1H, *J* = 7.9, 15.3), 5.61 (dt, 1H, *J* = 15.3, 6.8), 7.16-7.25 (m, 3H), 7.26-7.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 22.4, 22.8, 34.5, 43.7, 55.4, 57.8, 126.9, 128.7, 129.8, 130.0, 134.6, 137.2. MS (ESI): *m/z* 294 $[MH]^+$. Anal. Calcd for $C_{17}H_{27}NOS$: C, 69.58; H, 9.27; N, 4.77. Found: C, 69.46; H, 9.46; N, 4.56.



(R_S)-*N*-((*S*,*E*)-1-cyclohexyl-5-phenylpent-1-en-3-yl)-2-methylpropanesulfinamide (3.7k) Procedure D was followed using sulfinyl imine **3.2l** (59.3 mg, 0.250 mmol) and trifluoroborate **3.1b** (110 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.4:0.6 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 60.1 mg (69% yield, 99:1 dr) of **3.7k** as a white solid. mp 104.5-105.1 ºC. HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 16.6 min, t_{major} = 22.7 min. R_f = 0.37 (50% EtOAc/hexanes). IR 3204, 2920, 1448, 1048, 968 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.02-1.34 (m, 5H), 1.18 (s, 9H), 1.61-1.68 (m, 1H), 1.69-1.78 (m, 4H), 1.79-1.95 (m, 2H), 1.96-2.05 (m, 1H), 2.57-2.73 (m, 2H), 3.12 (s, 1H), 3.73-3.81 (m, 1H), 5.21 (dd, 1H, *J* = 8.1, 15.6), 5.62 (dd, 1H, *J* = 6.7, 15.6), 7.14-7.21 (m, 3H), 7.24-7.31 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.8, 26.2, 26.3, 32.2, 33.1, 38.6, 40.6, 55.4, 57.6, 126.1, 128.0, 128.6 (2C), 140.5, 141.7. MS (ESI): *m/z* 348 $[MH]^+$. Anal. Calcd for $C_{21}H_{33}NOS$: C, 72.57; H, 9.57; N, 4.03. Found: C, 72.67; H, 9.94; N, 3.91.

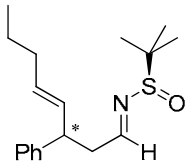


(R_S)-*N*-((*S*,*Z*)-1-phenylnon-4-en-3-yl)-2-methylpropanesulfinamide (3.7l). Procedure D was followed using sulfinyl imine **3.2l** (59.3 mg, 0.250 mmol) and trifluoroborate **3.1g** (95 mg, 0.50 mmol) in 2:3 DMF:H_2O (0.8:1.2 mL). The reaction mixture was stirred for 80 min. The short reaction time was important for minimizing isomerization of the product. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 56.2 mg (70% yield, 95:5 Z/E, 98:2 dr) of **3.7l** as a clear oil. The Z/E ratio was determined by ^1H NMR and the dr by HPLC (silica column, hexanes:*i*PrOH 98:2, 1.0 mL/min, λ = 222 nm, t_{minor} (R_S,*R* + E isomer)= 22.4 min, t_{major} (R_S,*S*)= 26.4 min). IR 3026, 2923, 1455, 1362, 1051, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, *J* = 7.0), 1.17 (s, 9H), 1.28-1.42 (m, 4H), 1.74-1.85 (m, 1H), 1.89-2.00 (m, 1H), 2.01-2.16 (m, 2H), 2.55-2.74 (m, 2H), 3.13 (d, 1H, *J* = 2.8), 4.15-4.23 (m, 1H), 5.22 (ddt, 1H, *J* = 9.6, 10.9, 1.5), 5.62 (dt, 1H, *J* = 7.6, 10.9), 7.14-7.22 (m, 3H), 7.23-7.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 22.6, 22.7, 27.8, 31.9, 32.2, 38.8, 51.8, 55.4, 126.2, 128.5, 128.6, 130.0, 134.2, 141.6. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{19}H_{32}NOS$, 322.2199; found, 322.2201.

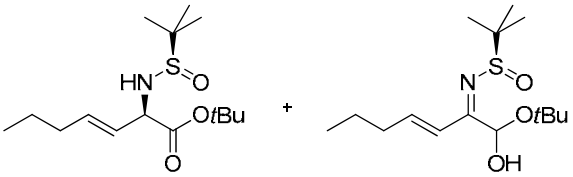


(R_S)-*N*-((*S*,*E*)-4-methyl-1-phenylhex-4-en-3-yl)-2-methylpropanesulfinamide (3.7m). Procedure D was followed using sulfinyl imine **3.2l** (59.3 mg, 0.250 mmol) and trifluoroborate

3.1c (0.081 g, 0.50 mmol) in 2:3 DMF:H_2O (0.4:0.6 mL). The reaction mixture was stirred for 20 h. Column chromatography (SiO_2, 10-50% EtOAc/hexanes) afforded 65.7 mg (90% yield, 96:4 dr) of **3.7m** as a white solid. mp 80.2-80.6 ºC. HPLC (silica column, hexanes:EtOH 98.5:1.5, 1.0 mL/min, λ = 210 nm): t_{minor} = 24.8 min, t_{major} = 25.8 min. IR 3206, 2923, 1454, 1306, 1046, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 9H), 1.54 (s, 3H), 1.66 (d, 3H, J = 6.8), 1.74-1.96 (m, 2H), 2.47-2.61 (m, 2H), 3.02 (s, 1H), 3.77-3.84 (m, 1H), 5.58 (q, 1H, J = 6.6), 7.13-7.21 (m, 3H), 7.23-7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 13.5, 22.8, 32.6, 36.2, 55.1, 62.5, 125.2, 126.2, 128.56, 128.62, 133.7, 141.7. MS (ESI): *m/z* 294 $[MH]^+$. Anal. Calcd for $C_{17}H_{27}NOS$: C, 69.58; H, 9.27; N, 4.77. Found: C, 69.45; H, 9.59; N, 4.83.

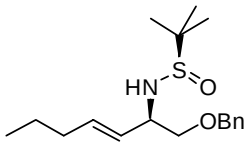


Sulfinamide (3.8). Procedure D was followed using sulfinyl imine **3.2s** (14.7 mg, 0.0625 mmol), trifluoroborate **3.1a** (22.0 mg, 0.125 mmol), hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (0.7 mg, 0.0016 mmol), 1,2-bis(diphenylphosphino)benzene (1.4 mg, 0.0031 mmol), and triethylamine (0.017 mL, 0.125 mmol) in 2:3 DMF:H_2O (0.2:0.3 mL). The reaction mixture was stirred for 20 h. The yield (72%) was determined by ^1H-NMR relative to an external standard. The diastereomeric ratio (66:33) was determined by ^1H-NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 1H, J = 7.3), 0.87 (t, 2H, J = 7.3), 1.06 (s, 6H), 1.08 (s, 3H), 3.35 (sextet, 0.7H, J = 7.3), 3.36 (sextet, 1.3H, J = 7.3), 1.92-2.01 (m, 2H), 2.86-3.01 (m, 2H), 3.72-3.82 (m, 1H), 5.44-5.53 (m, 1H), 5.54-5.64 (m, 1H), 7.16-7.23 (m, 3H), 7.27-7.31 (m, 2H), 7.99 (t, 0.7H, J = 4.8), 8.01 (t, 0.3H, J = 4.8).

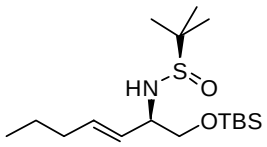


(R_S)-*N*-((*R*,*E*)-1-(*tert*-butyl)hept-3-enoate)-2-methylpropane-2-sulfinamide (3.9). In an inert atmosphere box, $[Rh(cod)(MeCN)_2]BF_4$ (4.9 mg, 0.013 mmol) was dissolved in DMF (1 mL, 0.25 M) and added to a vial containing 1,2-bis(diphenylphosphino)benzene (6.1 mg, 0.014 mmol). The resulting mixture of catalyst and ligand was added to a vial containing a stir-vane and the appropriate potassium alkenyltrifluoroborate (88.0 mg, 0.500 mmol) and 4Å molecular sieves (400 mg). To the mixture of catalyst, ligand, and trifluoroborate was added the sulfinyl imine **3.2t** (58.3 mg, 0.250 mmol) dissolved in DMF (1 mL, 0.25 M). The reaction vial was capped, removed from the inert atmosphere box, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C (aluminum block temperature) and stirred for 20 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 20-50% EtOAc/hexanes) afforded 21.0 mg (28% yield, 95:5 dr) of **3.9** as a clear oil. HPLC (silica

column, hexanes:*i*PrOH 97.5:2.5, 1.0 mL/min, λ = 210 nm): t_{minor} = 13.6 min, t_{major} = 15.9 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.3), 1.24 (s, 9H), 1.40 (sextet, 2H, *J* = 7.3), 1.45 (s, 9H), 2.03 (app q, 2H, *J* = 7.3), 4.18 (d, 1H, *J* = 4.3), 4.33-4.36 (m, 1H), 5.37 (ddt, 1H, *J* = 6.8, 15.2, 1.3), 5.77 (dtd, 1H, *J* = 15.2, 7.2, 1.2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 22.3, 22.7, 22.8, 28.1, 34.4, 55.9, 59.2, 126.0, 135.7, 171.0. HRMS-ESI (m/z): $[MNa]^+$ calcd for $C_{15}H_{29}NO_3SNa$, 326.1760; found, 326.1757. Column chromatography (SiO_2, 20-50% EtOAc/hexanes) also afforded 26.0 mg (34% yield, 70:30 dr) of byproduct **3.11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, *J* = 7.2), 0.97 (s, 9H), 1.47-1.56 (m, 2H), 1.48 (s, 9H), 2.18-2.29 (s, 2H), 3.37 (d, 0.3H, *J* = 10.4), 3.48 (d, 0.7H, *J* = 9.6), 4.41 (d, 0.7H, *J* = 9.6), 4.72 (d, 0.3H, *J* = 10.4), 5.99 (dt, 0.3H, *J* = 15.2, 1.6), 6.24 (dt, 0.7H, *J* = 14.8, 1.6), 6.42-6.56 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 21.7 (0.7C), 22.9 (0.3C), 26.7 (2.1C), 26.9 (0.9C), 28.1 (0.9C), 28.2, (2.1C), 33.8 (0.7C), 34.9 (0.3C), 58.9 (0.3C), 60.7 (0.7C), 66.1, 81.8 (0.3C), 82.2 (0.7C), 132.7 (0.3C), 133.4 (0.7C), 141.2 (0.7C), 142.4 (0.3C), 171.9 (0.7C), 172.2 (0.3C). MS (ESI): *m/z* 629 $[2MNa]^+$.

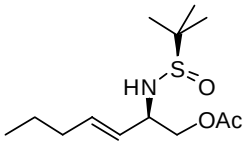


(R_S)-*N*-((*R*,*E*)-1-(benzyloxy)hept-3-en-2-yl)-2-methylpropane-2-sulfinamide (3.10a). Procedure H was followed using $[Rh(cod)(MeCN)_2]BF_4$ (2.4 mg, 0.0063 mmol), 1,2-bis(diphenylphosphino)benzene (2.8 mg, 0.0063 mmol), sulfinyl imine **3.2u** (31.7 mg, 0.125 mmol), trifluoroborate **3.1a** (44.0 mg, 0.250 mmol), and water (0.020 mL, 1.12 mmol) in DMF (1 mL). The reaction mixture was stirred for 20 h. The yield (63%) was determined by ^{1}H-NMR relative to an external standard. The diastereomeric ratio (91:9) was determined by ^{1}H-NMR analysis. IR 3210, 2957, 1732, 1454, 1362, 1227, 1067, 968 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.3), 1.20 (s, 9H), 1.39 (sextet, 2H, *J* = 7.3), 2.01 (app q, 2H, *J* = 7.3), 3.41 (dd, 1H, *J* = 9.6, 8.8), 3.52 (dd, 1H, *J* = 3.8, 9.6), 3.41 (d, 1H, *J* = 2.0), 4.05-4.11 (m, 1H), 4.48 (d, 1H, *J* = 12.0), 4.59 (d, 1H, *J* = 12.0), 5.19 (ddt, 1H, *J* = 7.8, 15.4, 1.5), 5.75 (dt, 1H, *J* = 15.4, 6.8), 7.27-7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.3, 22.8, 34.6, 55.4, 56.0, 72.9, 73.3, 127.08, 127.11, 128.0, 128.6, 136.0, 138.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{18}H_{30}NO_2S$, 324.1987; found, 324.1992.



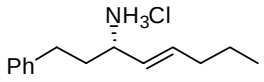
(R_S)-*N*-((*R*,*E*)-1-(tert-butyldimethylsilyloxy)hept-3-en-2-yl)-2-methylpropane-2-sulfinamide (3.10b). Procedure H was followed using $[Rh(cod)(MeCN)_2]BF_4$ (2.4 mg, 0.0063 mmol), 1,2-bis(diphenylphosphino)benzene (2.8 mg, 0.0063 mmol), sulfinyl imine **3.2v** (34.7 mg, 0.125 mmol), trifluoroborate **3.1a** (44.0 mg, 0.250 mmol), and water (0.020 mL, 1.12 mmol) in DMF (1 mL). The reaction mixture was stirred for 20 h. The yield (77%) was determined by ^{1}H-NMR relative to an external standard. The diastereomeric ratio (88:12) was determined by ^{1}H-NMR analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.79-0.93 (m, 12H), 1.20 (s, 9H),

1.40 (sextet, 2H, J = 7.5), 2.01 (app q, 2H, J = 6.6), 3.44 (app t, 1H, J = 9.3), 3.64 (dd, 1H, J = 4.2, 9.6), 3.83-3.99 (m, 2H), 5.15 (dd, 1H, J = 8.1, 15.0), 5.76 (td, 1H, J = 6.6, 15.0). MS (ESI): *m/z* 348 $[MH]^+$.



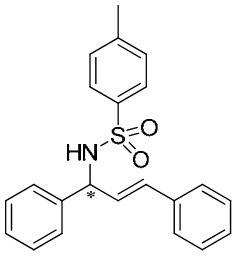
(R_S)-*N*-((*R*,*E*)-1-(acyloxy)hept-3-en-2-yl)-2-methylpropane-2-sulfinamide (3.10c). Procedure H was followed using $[Rh(cod)(MeCN)_2]BF_4$ (2.4 mg, 0.0063 mmol), 1,2-bis(diphenylphosphino)benzene (2.8 mg, 0.0063 mmol), sulfinyl imine **3.2w** (25.7 mg, 0.125 mmol), trifluoroborate **3.1a** (44.0 mg, 0.250 mmol), and water (0.020 mL, 1.12 mmol) in DMF (1 mL). The reaction mixture was stirred for 20 h. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 20.4 mg (59% yield, 96:4 dr) of **3.10c** as a clear oil. HPLC (silica column, hexanes:*i*PrOH 95:5, 1.0 mL/min, λ = 210 nm): t_{minor} = 12.7 min, t_{major} = 16.2 min. IR 3209, 2958, 1740, 1457, 1363, 1227, 1045, 969 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.4), 1.20 (s, 9H), 1.39 (sextet, 2H, J = 7.4), 2.02 (app q, 2H, J = 7.4), 2.08 (s, 3H), 3.54 (d, 1H, J = 3.2), 3.98 (dd, 1H, J = 8.4, 10.9), 4.04-4.08 (m, 1H), 4.18 (dd, 1H, J = 3.8, 10.9), 5.22 (ddt, 1H, J = 7.6, 15.4, 1.2), 5.77 (dt, 1H, J = 15.4, 6.8). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.8, 21.1, 22.3, 22.8, 34.6, 55.7, 56.5, 67.2, 126.2, 136.5, 171.2. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{13}H_{26}NO_3S$, 276.1628; found, 276.1632.

Synthesis of α-Branched Allylic Amine by Cleavage of *tert*-Butanesulfinyl Group

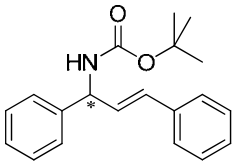


(*S*,*E*)-1-phenyloct-4-en-3-amine hydrochloride (3.12). This procedure was adapted from Plobeck.[38] *N*-Sulfinyl allylic amine **3.7d** (100 mg, 0.325 mmol) was treated with a 1:1 (v/v) mixture of MeOH and 4.0M HCl in dioxane (3.2 mL; 0.1M) at room temperature for 1 h. The reaction mixture was concentrated to dryness and precipitated with pentane. The precipitate was collected by filtration and washed with pentane to afford 74.4 mg (96%) of amine hydrochloride **3.12** as an off-white solid. The amine hydrochloride was derivatized with an excess of (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride according to Mosher's procedure.[56] Ratios of the MTPA diastereomers were determined by HPLC analysis. HPLC (silica column, hexanes:methyl *tert*-butyl ether 97:3, 1.0 mL/min, λ = 210 nm): t (R_{MTPA}, S; S_{MTPA}, R) = 21.3 min, t (R_{MTPA}, R; S_{MTPA}, S) = 24.1 min. mp 202.8-203.4 ºC. $[\alpha]_D^{23}$ +20.7º (*c* 1.0, MeOH). ^1H NMR (500 MHz, MeOD): δ 0.97 (t, 3H, J = 7.3), 1.49 (sextet, 2H, J = 7.3), 1.86-1.96 (m, 1H), 1.99-2.08 (m, 1H), 2.13 (app q, 2H, J = 7.3), 2.56-2.65 (m, 1H), 2.67-2.75 (m, 1H), 3.63 (dt, 1H, J = 4.7, 9.3), 5.45 (ddt, 1H, J = 8.7, 15.3, 1.4), 5.91 (dt, 1H, J = 6.9, 15.3), 7.16-7.23 (m, 3H), 7.26-7.32 (m, 2H). ^{13}C NMR (100 MHz, MeOD): δ 14.0, 23.1, 32.6, 35.4, 36.0, 54.7, 126.8, 127.3, 129.4, 129.6, 139.8, 141.7. MS (ESI): *m/z* 204 $[MH]^+$. Anal. Calcd for $C_{14}H_{22}ClN$: C, 70.13; H, 9.25; N, 5.84. Found: C, 69.82; H, 9.59; N, 5.62.

Synthesis of α-Branched *N*-Boc and *N*-Tosyl Allylic Amines



***N*-Tosyl allylic amine (3.13).** The reaction was set up in a glovebox. $[Rh(cod)(MeCN)_2]BF_4$ (4.9 mg, 0.013 mmol) was dissolved in dioxane (0.5 mL) and added to a vial containing (*R*,*R*)-deguphos (7.3 mg, 0.014 mmol). The resulting mixture of catalyst and ligand was added to a vial containing a stir-vane, commercially available cinnamyl trifluoroborate **3.1h** (52.5 mg, 0.250 mmol), and 4Å molecular sieves (200 mg). To the mixture of catalyst, ligand, and trifluoroborate was added *N*-tosyl benzaldimine (32.4 mg, 0.125 mmol) dissolved in dioxane (0.5 mL). The reaction vial was capped, removed from the glovebox, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C (aluminum block temperature) and stirred for 20 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (10 mL). The organic layer was washed with water (5 mL) and the aqueous layer was extracted with 20% EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 15% EtOAc/hexanes) afforded 33.1 mg (73% yield, 4% ee) of **3.13**. Authentic mixtures of enantiomers were obtained by performing the above reaction with an achiral phosphine ligand (dppbenz), and the ratios of the enantiomers were determined by chiral HPLC analysis. HPLC (Daicel AS column, hexanes:*i*PrOH 88:12, 1.0 mL/min, λ = 210 nm): t_{minor} = 42.8 min, t_{major}= 48.4 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 4.90 (d, 1H, *J* = 7.1), 5.11 (app t, 1H, *J* = 6.8), 6.08 (dd, 1H, *J* = 6.6, 15.7), 6.35 (d, 1H, *J* = 16.0), 7.11-7.30 (m, 12H), 7.65 (d, 2H, *J* = 8.3). MS (ESI): *m/z* 386 $[MNa]^+$.



***N*-Boc allylic amine 3.14.**

- The reaction was set up in a glovebox. $[Rh(cod)(MeCN)_2]BF_4$ (4.9 mg, 0.013 mmol) was dissolved in dioxane (0.5 mL) and added to a vial containing (*R*,*R*)-deguphos (7.3 mg, 0.014 mmol). The resulting mixture of catalyst and ligand was added to a vial containing a stir-vane, commercially available cinnamyl trifluoroborate **3.1h** (52.5 mg, 0.250 mmol), and 4Å molecular sieves (200 mg). To the mixture of catalyst, ligand, and trifluoroborate was added *N*-Boc benzaldimine (25.7 mg, 0.125 mmol) dissolved in dioxane (0.5 mL). The reaction vial was capped, removed from the glovebox, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C (aluminum block temperature) and stirred for 20 h. The reaction mixture was allowed to cool to rt and diluted with EtOAc (10 mL). The organic

layer was washed with water (5 mL) and the aqueous layer was extracted with 20% EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 5-10% EtOAc/hexanes) afforded 27.3 mg (71% yield, 6% ee) of **3.x**. Authentic mixtures of enantiomers were obtained by performing the above reaction with an achiral phosphine ligand (dppbenz), and the ratio of the enantiomers were determined by chiral HPLC analysis. HPLC (Daicel AD column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{major} = 17.6 min, t_{minor}= 20.5 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H), 4.85 (br s, 1H), 5.38-5.52 (br s, 1H), 6.32 (dd, 1H, *J* = 5.6, 16.0), 6.54 (d, 1H, *J* = 16.0), 7.19-7.42 (m, 10H). MS (ESI): *m/z* 332 $[MNa]^+$.

- The reaction was set up in a glovebox. $[Rh(cod)(MeCN)_2]BF_4$ (2.5 mg, 0.008 mmol) was dissolved in dioxane (0.25 mL) and added to a vial containing phosphoramidite **3.15**[57] (7.0 mg, 0.014 mmol). The resulting mixture of catalyst and ligand was added to a vial containing a stir-vane, commercially available cinnamyl trifluoroborate **3.1h** (26.2 mg, 0.125 mmol), and 4Å molecular sieves (100 mg). To the mixture of catalyst, ligand, and trifluoroborate was added *N*-Boc-α-(phenylsulfonyl)benzylamine **3.16** (25.7 mg, 0.125 mmol) dissolved in dioxane (0.25 mL), followed by triethylamine (0.013 mL, 0.094 mmol), and K_2CO_3 (52.0 mg, 0.375 mmol). The reaction vial was capped, removed from the glovebox, and placed in a heating block on the benchtop with stirring. The reaction mixture was heated to 60 °C (aluminum block temperature) and stirred for 20 h. The reaction mixture was allowed to cool to rt and filtered through a pad of Celite. The Celite was washed with EtOAc (4 x 10 mL), and the filtrates were combined and concentrated. The yield (44%) and the ratio of the enantiomers were determined by chiral HPLC analysis. HPLC (Daicel AD column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{major} = 17.2 min, t_{minor}= 19.9 min. ^{1}H NMR and HPLC data corresponded to the data reported for the procedure above.

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(27) The addition of vinyltrifluoroborate (13%) and vinyl MIDA boronate (11%) to imine **3.2a** proceed in low yields. The vinyl boron reagents most likely failed to couple efficiently due to their electron-deficient as well as unstable nature.

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Appendix 3.1: X-ray Crystal Data for 3.3m

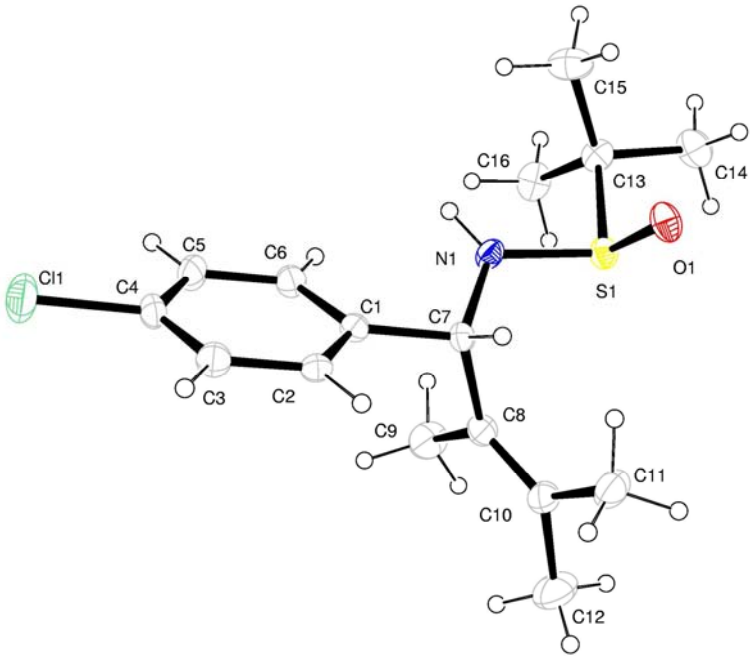


Figure A3.1.1 X-ray crystal structure of **3.3m** with thermal ellipsoids drawn at the 50% probability level.

Data collection paramaters. A colorless plate 0.15 x 0.12 x 0.04 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 130(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 99.9% complete to 25.00° in θ. A total of 19116 reflections were collected covering the indices, -12<=*h*<=12, -13<=*k*<=13, -13<=*l*<=13. 7327 reflections were found to be symmetry independent, with an R_{int} of 0.0474. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P1 (No. 1). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. Absolute stereochemistry at C7 and C23 was determined to be S in both cases.

Table A3.1.1. Crystal data and structure refinement for **3.3m**

Empirical formula	$C_{16}H_{24}ClNOS$	
Formula weight	313.87	
Temperature	130(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.6892(10) Å	α = 78.256(2)°.
	b = 9.9873(10) Å	β = 64.7200(10)°.
	c = 10.4863(11) Å	γ = 75.357(2)°.
Volume	882.45(16) $Å^3$	
Z	2	
Density (calculated)	1.181 Mg/m^3	
Absorption coefficient	0.331 mm^{-1}	
F(000)	336	
Crystal size	0.15 x 0.12 x 0.04 mm^3	
Crystal color/habit	colorless plate	
Theta range for data collection	2.12 to 28.29°.	
Index ranges	-12<=h<=12, -13<=k<=13, -13<=l<=13	
Reflections collected	19116	
Independent reflections	7327 [R(int) = 0.0474]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9869 and 0.9520	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7327 / 3 / 373	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0534, wR2 = 0.1047	
R indices (all data)	R1 = 0.0841, wR2 = 0.1213	
Absolute structure parameter	-0.06(6)	
Largest diff. peak and hole	0.330 and -0.281 $e.Å^{-3}$	

Table A3.1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **3.3m**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

atom	x	y	z	U(eq)
C(1)	9412(4)	11378(3)	2845(4)	28(1)
C(2)	9974(4)	12104(3)	3458(4)	32(1)
C(3)	11183(4)	12802(4)	2656(4)	37(1)
C(4)	11822(4)	12793(4)	1201(4)	38(1)
C(5)	11299(5)	12091(4)	543(4)	40(1)
C(6)	10091(4)	11381(4)	1378(4)	34(1)
C(7)	8099(4)	10608(3)	3780(4)	28(1)
C(8)	6521(4)	11547(4)	4058(4)	33(1)
C(9)	6207(5)	12175(5)	2745(4)	50(1)
C(10)	5505(4)	11817(4)	5366(4)	38(1)
C(11)	5695(5)	11130(5)	6708(4)	49(1)
C(12)	3999(5)	12853(5)	5630(5)	65(1)
C(13)	7473(4)	7161(4)	2786(4)	35(1)
C(14)	6304(5)	6170(4)	3538(5)	49(1)
C(15)	9126(5)	6346(4)	2421(5)	52(1)
C(16)	7217(5)	7967(5)	1489(4)	45(1)
C(17)	11748(4)	7222(4)	4579(4)	29(1)
C(18)	12158(4)	6342(4)	3555(4)	36(1)
C(19)	12938(4)	6749(4)	2122(4)	39(1)
C(20)	13274(4)	8068(4)	1713(4)	36(1)
C(21)	12850(4)	8986(4)	2683(4)	40(1)
C(22)	12087(4)	8555(4)	4122(4)	36(1)
C(23)	11023(4)	6697(3)	6153(4)	30(1)
C(24)	10563(4)	7813(3)	7123(4)	27(1)
C(25)	9029(4)	8771(4)	7306(4)	39(1)
C(26)	11512(4)	7988(4)	7672(4)	35(1)
C(27)	13108(4)	7110(4)	7427(5)	46(1)
C(28)	11133(5)	9135(4)	8574(4)	44(1)
C(29)	7909(4)	4141(4)	8050(4)	35(1)
C(30)	7357(5)	4988(4)	9289(4)	53(1)
C(31)	8021(5)	2587(4)	8554(4)	43(1)

C(32)	6934(5)	4586(4)	7167(5)	46(1)
N(1)	8262(3)	9382(3)	3101(3)	30(1)
N(2)	9708(3)	6019(3)	6487(3)	30(1)
O(1)	7347(3)	7578(3)	5274(3)	39(1)
O(2)	10370(3)	3570(3)	5689(3)	42(1)
S(1)	6949(1)	8380(1)	4076(1)	31(1)
S(2)	9939(1)	4326(1)	6917(1)	31(1)
Cl(1)	13369(1)	13659(1)	160(1)	68(1)
Cl(2)	14282(1)	8589(1)	-78(1)	50(1)

Table A3.1.3. Bond lengths [Å] for **3.3m**

bond	angle	bond	angle
C(1)-C(2)	1.387(5)	C(18)-C(19)	1.390(5)
C(1)-C(6)	1.390(5)	C(18)-H(18)	0.9500
C(1)-C(7)	1.515(5)	C(19)-C(20)	1.376(5)
C(2)-C(3)	1.378(5)	C(19)-H(19)	0.9500
C(2)-H(2)	0.9500	C(20)-C(21)	1.370(5)
C(3)-C(4)	1.380(5)	C(20)-Cl(2)	1.745(4)
C(3)-H(3)	0.9500	C(21)-C(22)	1.397(5)
C(4)-C(5)	1.379(5)	C(21)-H(21)	0.9500
C(4)-Cl(1)	1.749(4)	C(22)-H(22)	0.9500
C(5)-C(6)	1.390(5)	C(23)-N(2)	1.471(4)
C(5)-H(5)	0.9500	C(23)-C(24)	1.517(5)
C(6)-H(6)	0.9500	C(23)-H(23)	1.0000
C(7)-N(1)	1.480(4)	C(24)-C(26)	1.335(5)
C(7)-C(8)	1.519(5)	C(24)-C(25)	1.508(5)
C(7)-H(7)	1.0000	C(25)-H(25A)	0.9800
C(8)-C(10)	1.336(5)	C(25)-H(25B)	0.9800
C(8)-C(9)	1.514(5)	C(25)-H(25C)	0.9800
C(9)-H(9A)	0.9800	C(26)-C(28)	1.507(5)
C(9)-H(9B)	0.9800	C(26)-C(27)	1.514(5)
C(9)-H(9C)	0.9800	C(27)-H(27A)	0.9800
C(10)-C(11)	1.500(5)	C(27)-H(27B)	0.9800

C(10)-C(12)	1.512(5)	C(27)-H(27C)	0.9800
C(11)-H(11A)	0.9800	C(28)-H(28A)	0.9800
C(11)-H(11B)	0.9800	C(28)-H(28B)	0.9800
C(11)-H(11C)	0.9800	C(28)-H(28C)	0.9800
C(12)-H(12A)	0.9800	C(29)-C(30)	1.521(6)
C(12)-H(12B)	0.9800	C(29)-C(32)	1.522(5)
C(12)-H(12C)	0.9800	C(29)-C(31)	1.526(5)
C(13)-C(16)	1.517(5)	C(29)-S(2)	1.847(4)
C(13)-C(15)	1.522(5)	C(30)-H(30A)	0.9800
C(13)-C(14)	1.540(5)	C(30)-H(30B)	0.9800
C(13)-S(1)	1.828(4)	C(30)-H(30C)	0.9800
C(14)-H(14A)	0.9800	C(31)-H(31A)	0.9800
C(14)-H(14B)	0.9800	C(31)-H(31B)	0.9800
C(14)-H(14C)	0.9800	C(31)-H(31C)	0.9800
C(15)-H(15A)	0.9800	C(32)-H(32A)	0.9800
C(15)-H(15B)	0.9800	C(32)-H(32B)	0.9800
C(15)-H(15C)	0.9800	C(32)-H(32C)	0.9800
C(16)-H(16A)	0.9800	N(1)-S(1)	1.668(3)
C(16)-H(16B)	0.9800	N(1)-H(1)	0.8800
C(16)-H(16C)	0.9800	N(2)-S(2)	1.642(3)
C(17)-C(18)	1.388(5)	N(2)-H(2A)	0.8800
C(17)-C(22)	1.391(5)	O(1)-S(1)	1.488(3)
C(17)-C(23)	1.529(5)	O(2)-S(2)	1.476(3)

Table A3.1.4. Bond angles [°] for **3.3m**

bond	angle	bond	angle
C(2)-C(1)-C(6)	118.2(3)	C(20)-C(19)-C(18)	119.0(4)
C(2)-C(1)-C(7)	119.5(3)	C(20)-C(19)-H(19)	120.5
C(6)-C(1)-C(7)	122.3(3)	C(18)-C(19)-H(19)	120.5
C(3)-C(2)-C(1)	121.7(3)	C(21)-C(20)-C(19)	121.5(3)
C(3)-C(2)-H(2)	119.1	C(21)-C(20)-Cl(2)	118.8(3)
C(1)-C(2)-H(2)	119.1	C(19)-C(20)-Cl(2)	119.7(3)
C(2)-C(3)-C(4)	118.5(3)	C(20)-C(21)-C(22)	118.9(4)
C(2)-C(3)-H(3)	120.7	C(20)-C(21)-H(21)	120.6

C(4)-C(3)-H(3)	120.7	C(22)-C(21)-H(21)	120.6
C(5)-C(4)-C(3)	121.8(3)	C(17)-C(22)-C(21)	121.3(4)
C(5)-C(4)-Cl(1)	118.7(3)	C(17)-C(22)-H(22)	119.3
C(3)-C(4)-Cl(1)	119.4(3)	C(21)-C(22)-H(22)	119.3
C(4)-C(5)-C(6)	118.5(4)	N(2)-C(23)-C(24)	110.9(3)
C(4)-C(5)-H(5)	120.7	N(2)-C(23)-C(17)	112.2(3)
C(6)-C(5)-H(5)	120.7	C(24)-C(23)-C(17)	113.2(3)
C(5)-C(6)-C(1)	121.2(3)	N(2)-C(23)-H(23)	106.7
C(5)-C(6)-H(6)	119.4	C(24)-C(23)-H(23)	106.7
C(1)-C(6)-H(6)	119.4	C(17)-C(23)-H(23)	106.7
N(1)-C(7)-C(1)	108.9(3)	C(26)-C(24)-C(25)	123.3(3)
N(1)-C(7)-C(8)	111.1(3)	C(26)-C(24)-C(23)	121.8(3)
C(1)-C(7)-C(8)	111.6(3)	C(25)-C(24)-C(23)	114.7(3)
N(1)-C(7)-H(7)	108.4	C(24)-C(25)-H(25A)	109.5
C(1)-C(7)-H(7)	108.4	C(24)-C(25)-H(25B)	109.5
C(8)-C(7)-H(7)	108.4	H(25A)-C(25)-H(25B)	109.5
C(10)-C(8)-C(9)	122.8(3)	C(24)-C(25)-H(25C)	109.5
C(10)-C(8)-C(7)	122.2(3)	H(25A)-C(25)-H(25C)	109.5
C(9)-C(8)-C(7)	115.0(3)	H(25B)-C(25)-H(25C)	109.5
C(8)-C(9)-H(9A)	109.5	C(24)-C(26)-C(28)	123.3(3)
C(8)-C(9)-H(9B)	109.5	C(24)-C(26)-C(27)	124.8(3)
H(9A)-C(9)-H(9B)	109.5	C(28)-C(26)-C(27)	111.9(3)
C(8)-C(9)-H(9C)	109.5	C(26)-C(27)-H(27A)	109.5
H(9A)-C(9)-H(9C)	109.5	C(26)-C(27)-H(27B)	109.5
H(9B)-C(9)-H(9C)	109.5	H(27A)-C(27)-H(27B)	109.5
C(8)-C(10)-C(11)	125.0(3)	C(26)-C(27)-H(27C)	109.5
C(8)-C(10)-C(12)	122.0(4)	H(27A)-C(27)-H(27C)	109.5
C(11)-C(10)-C(12)	113.0(4)	H(27B)-C(27)-H(27C)	109.5
C(10)-C(11)-H(11A)	109.5	C(26)-C(28)-H(28A)	109.5
C(10)-C(11)-H(11B)	109.5	C(26)-C(28)-H(28B)	109.5
H(11A)-C(11)-H(11B)	109.5	H(28A)-C(28)-H(28B)	109.5
C(10)-C(11)-H(11C)	109.5	C(26)-C(28)-H(28C)	109.5
H(11A)-C(11)-H(11C)	109.5	H(28A)-C(28)-H(28C)	109.5
H(11B)-C(11)-H(11C)	109.5	H(28B)-C(28)-H(28C)	109.5
C(10)-C(12)-H(12A)	109.5	C(30)-C(29)-C(32)	113.9(3)

C(10)-C(12)-H(12B)	109.5	C(30)-C(29)-C(31)	111.0(3)
H(12A)-C(12)-H(12B)	109.5	C(32)-C(29)-C(31)	110.5(3)
C(10)-C(12)-H(12C)	109.5	C(30)-C(29)-S(2)	107.4(3)
H(12A)-C(12)-H(12C)	109.5	C(32)-C(29)-S(2)	109.5(3)
H(12B)-C(12)-H(12C)	109.5	C(31)-C(29)-S(2)	104.1(3)
C(16)-C(13)-C(15)	112.5(4)	C(29)-C(30)-H(30A)	109.5
C(16)-C(13)-C(14)	109.4(3)	C(29)-C(30)-H(30B)	109.5
C(15)-C(13)-C(14)	110.1(3)	H(30A)-C(30)-H(30B)	109.5
C(16)-C(13)-S(1)	108.5(3)	C(29)-C(30)-H(30C)	109.5
C(15)-C(13)-S(1)	111.9(3)	H(30A)-C(30)-H(30C)	109.5
C(14)-C(13)-S(1)	104.1(3)	H(30B)-C(30)-H(30C)	109.5
C(13)-C(14)-H(14A)	109.5	C(29)-C(31)-H(31A)	109.5
C(13)-C(14)-H(14B)	109.5	C(29)-C(31)-H(31B)	109.5
H(14A)-C(14)-H(14B)	109.5	H(31A)-C(31)-H(31B)	109.5
C(13)-C(14)-H(14C)	109.5	C(29)-C(31)-H(31C)	109.5
H(14A)-C(14)-H(14C)	109.5	H(31A)-C(31)-H(31C)	109.5
H(14B)-C(14)-H(14C)	109.5	H(31B)-C(31)-H(31C)	109.5
C(13)-C(15)-H(15A)	109.5	C(29)-C(32)-H(32A)	109.5
C(13)-C(15)-H(15B)	109.5	C(29)-C(32)-H(32B)	109.5
H(15A)-C(15)-H(15B)	109.5	H(32A)-C(32)-H(32B)	109.5
C(13)-C(15)-H(15C)	109.5	C(29)-C(32)-H(32C)	109.5
H(15A)-C(15)-H(15C)	109.5	H(32A)-C(32)-H(32C)	109.5
H(15B)-C(15)-H(15C)	109.5	H(32B)-C(32)-H(32C)	109.5
C(13)-C(16)-H(16A)	109.5	C(7)-N(1)-S(1)	113.8(2)
C(13)-C(16)-H(16B)	109.5	C(7)-N(1)-H(1)	123.1
H(16A)-C(16)-H(16B)	109.5	S(1)-N(1)-H(1)	123.1
C(13)-C(16)-H(16C)	109.5	C(23)-N(2)-S(2)	117.9(2)
H(16A)-C(16)-H(16C)	109.5	C(23)-N(2)-H(2A)	121.0
H(16B)-C(16)-H(16C)	109.5	S(2)-N(2)-H(2A)	121.0
C(18)-C(17)-C(22)	117.8(3)	O(1)-S(1)-N(1)	109.28(15)
C(18)-C(17)-C(23)	120.1(3)	O(1)-S(1)-C(13)	106.89(16)
C(22)-C(17)-C(23)	122.0(3)	N(1)-S(1)-C(13)	98.11(16)
C(17)-C(18)-C(19)	121.5(4)	O(2)-S(2)-N(2)	111.81(16)
C(17)-C(18)-H(18)	119.2	O(2)-S(2)-C(29)	104.83(17)
C(19)-C(18)-H(18)	119.2	N(2)-S(2)-C(29)	100.40(15)

Table A3.1.5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **3.3m**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(2)	26(2)	29(2)	-1(1)	-12(2)	-3(1)
C(2)	33(2)	29(2)	29(2)	-10(2)	-7(2)	-5(2)
C(3)	42(2)	37(2)	33(2)	-10(2)	-13(2)	-10(2)
C(4)	39(2)	32(2)	38(2)	-5(2)	-3(2)	-17(2)
C(5)	45(2)	42(2)	25(2)	-4(2)	-3(2)	-16(2)
C(6)	38(2)	34(2)	29(2)	-4(2)	-12(2)	-10(2)
C(7)	30(2)	26(2)	24(2)	2(1)	-9(2)	-8(1)
C(8)	35(2)	31(2)	32(2)	2(2)	-16(2)	-4(2)
C(9)	49(3)	56(3)	41(3)	1(2)	-23(2)	2(2)
C(10)	31(2)	37(2)	39(2)	-1(2)	-11(2)	-3(2)
C(11)	42(2)	56(3)	33(2)	-1(2)	-6(2)	-2(2)
C(12)	41(3)	70(3)	63(3)	-12(3)	-11(2)	13(2)
C(13)	29(2)	44(2)	39(2)	-6(2)	-18(2)	-7(2)
C(14)	59(3)	44(2)	56(3)	-6(2)	-29(2)	-20(2)
C(15)	45(2)	50(2)	71(3)	-25(2)	-30(2)	2(2)
C(16)	48(2)	61(3)	37(2)	-4(2)	-22(2)	-18(2)
C(17)	23(2)	37(2)	28(2)	-6(2)	-11(1)	-2(1)
C(18)	33(2)	42(2)	37(2)	-7(2)	-16(2)	-12(2)
C(19)	36(2)	56(2)	29(2)	-13(2)	-8(2)	-15(2)
C(20)	24(2)	54(2)	27(2)	-2(2)	-9(2)	-4(2)
C(21)	42(2)	36(2)	37(2)	2(2)	-15(2)	-4(2)
C(22)	38(2)	34(2)	33(2)	-5(2)	-11(2)	-4(2)
C(23)	24(2)	33(2)	32(2)	-7(2)	-11(2)	-1(1)
C(24)	25(2)	29(2)	25(2)	-7(1)	-9(2)	-2(1)
C(25)	36(2)	43(2)	39(2)	-13(2)	-19(2)	6(2)
C(26)	33(2)	37(2)	32(2)	-7(2)	-10(2)	-7(2)
C(27)	37(2)	55(3)	52(3)	-18(2)	-24(2)	-1(2)
C(28)	40(2)	50(2)	45(3)	-19(2)	-17(2)	-4(2)
C(29)	32(2)	32(2)	32(2)	4(2)	-7(2)	-6(2)
C(30)	60(3)	42(2)	36(2)	-10(2)	3(2)	-11(2)
C(31)	53(2)	32(2)	42(2)	8(2)	-23(2)	-9(2)

C(32)	34(2)	45(2)	56(3)	17(2)	-21(2)	-14(2)
N(1)	28(2)	36(2)	24(2)	-8(1)	-4(1)	-9(1)
N(2)	25(2)	33(2)	32(2)	-5(1)	-14(1)	-1(1)
O(1)	47(2)	38(1)	39(2)	8(1)	-25(1)	-15(1)
O(2)	38(2)	49(2)	36(2)	-18(1)	-7(1)	-6(1)
S(1)	30(1)	32(1)	31(1)	2(1)	-14(1)	-8(1)
S(2)	31(1)	31(1)	32(1)	-7(1)	-14(1)	-1(1)
Cl(1)	63(1)	71(1)	57(1)	-18(1)	10(1)	-43(1)
Cl(2)	39(1)	74(1)	31(1)	1(1)	-14(1)	-10(1)

Table A3.1.6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **3.3m**

atom	x	y	z	U(eq)
H(2)	9513	12120	4458	38
H(3)	11569	13279	3093	44
H(5)	11755	12091	-459	48
H(6)	9722	10890	939	40
H(7)	8194	10271	4710	33
H(9A)	5087	12496	3014	75
H(9B)	6590	11471	2084	75
H(9C)	6742	12965	2288	75
H(11A)	6531	10311	6500	74
H(11B)	4723	10843	7392	74
H(11C)	5956	11788	7110	74
H(12A)	3732	13315	6466	98
H(12B)	3168	12365	5793	98
H(12C)	4119	13549	4801	98
H(14A)	5243	6710	3816	73
H(14B)	6457	5661	4386	73
H(14C)	6467	5507	2892	73
H(15A)	9298	5587	1876	78
H(15B)	9281	5959	3298	78
H(15C)	9863	6968	1854	78

H(16A)	8016	8539	966	68
H(16B)	6188	8569	1788	68
H(16C)	7280	7313	876	68
H(18)	11901	5441	3840	43
H(19)	13233	6127	1436	47
H(21)	13072	9900	2383	48
H(22)	11793	9184	4801	44
H(23)	11840	5966	6364	36
H(25A)	8276	8608	8281	59
H(25B)	8644	8588	6644	59
H(25C)	9170	9741	7110	59
H(27A)	13154	6692	8342	68
H(27B)	13896	7698	6934	68
H(27C)	13307	6372	6847	68
H(28A)	11796	9824	8039	66
H(28B)	11316	8741	9436	66
H(28C)	10040	9584	8834	66
H(30A)	7198	5982	8955	79
H(30B)	8140	4773	9695	79
H(30C)	6375	4753	10016	79
H(31A)	8691	2310	9084	64
H(31B)	8462	2059	7732	64
H(31C)	6982	2395	9171	64
H(32A)	5904	4347	7724	69
H(32B)	7446	4104	6310	69
H(32C)	6825	5594	6898	69
H(1)	8985	9200	2260	36
H(2A)	8825	6505	6458	36

Chapter 4. General One-Pot Method for the Preparation of *N*-*tert*-Butanesulfinylamine Diastereomer Mixtures as Standards for Stereoselectivity Determinations.

A one-pot preparation of N-sulfinylamine diastereomer mixtures is presented that proceeds in excellent yields (84−98%) for a diverse set of N-sulfinyl imine addition products. The method is operationally simple and extractive isolation provides analytically pure mixtures of diastereomers as standards for the rapid and accurate determination of N-sulfinylamine diastereomeric purity. The majority of this work was published in a communication (Brak, K.; Barrett, K. T.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 3606-3608).

Authorship

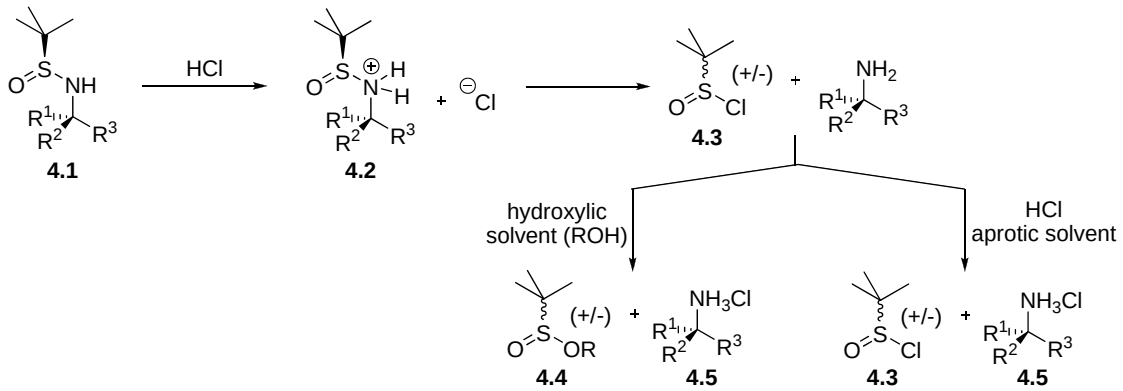
The development of a one-pot method for the formation of authentic mixtures of *N*-sulfinylamine diastereomers was conducted in collaboration with Kimberly Barrett, an undergraduate who I mentored.

Introduction

The asymmetric synthesis of chiral, α-branched amines is an important and heavily pursued endeavor due to the high frequency with which this structural motif occurs in drugs and natural products.[1] Additions of nucleophiles to enantiomerically pure *N*-*tert*-butanesulfinyl imines are among the most popular approaches for the asymmetric synthesis of amines.[2] However, to rigorously determine the diastereoselectivity of the nucleophilic addition step, further derivatization of the product is often necessary to obtain standards for the analysis of stereoisomeric purity. Typically, cleavage of the *tert*-butanesulfinyl group is followed by isolation and then reaction of the resulting amine with a derivatization reagent such as racemic sulfinyl chloride or both (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[3] These multi-step procedures are tedious and require the use of expensive reagents of limited stability. We report in this chapter a general and easy-to-perform one-pot method for the preparation of *N*-*tert*-butanesulfinyl amine diastereomer mixtures.

The HCl-mediated cleavage of the *tert*-butanesulfinyl group is thought to proceed by an acid-base reaction to provide **4.2**, followed by attack of chloride anion at the electrophilic sulfur to produce the configurationally unstable *tert*-butanesulfinyl chloride (**4.3**) (Scheme 4.1).[4] The deprotection of an *N*-sulfinyl amine **4.1** to provide the amine hydrochloride **4.5** is generally carried out in the presence of a hydroxylic cosolvent, which reacts rapidly in situ with the sulfinyl chloride to give sulfinate ester **4.4** as a byproduct.[3a] However, we have recently demonstrated that by carrying out the HCl-mediated cleavage in an aprotic solvent, racemic sulfinyl chloride **4.3** is generated in near quantitative yield.[4] Based upon this observation, we envisioned that authentic diastereomers of *N*-*tert*-butanesulfinyl amines could readily be formed in one-pot by HCl mediated sulfinyl group cleavage in an aprotic solvent followed by addition of base to the same reaction vessel without any workup to achieve re-sulfinylation of the amine.

Scheme 4.1. Mechanism of acid-catalyzed cleavage of **4.1** in hydroxylic versus aprotic solvent

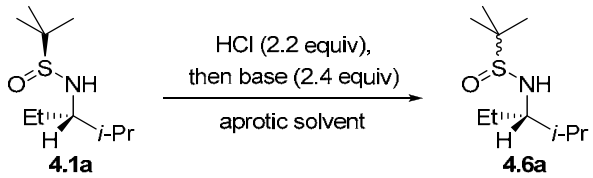


One-Pot Preparation of *N*-*tert*-Butanesulfinylamine Diastereomer Mixtures

Reaction Optimization

In order to explore the hypothesis proposed in the introduction, *N*-sulfinyl amine **4.1a** was treated with HCl at room temperature followed by addition of triethylamine at -78 ºC (Table 4.1, entry 1). Gratifyingly, the *N*-sulfinyl amine diastereomer mixture **4.6a** was obtained in quantitative yield and with 65:35 dr. Furthermore, it was found that cooling the reaction mixture prior to the addition of base was unnecessary, with a high yield and an approximate 1:1 mixture of *N*-sulfinyl amine diastereomers obtained at room temperature (entry 2). While the reaction proceeded in high yield (77-99%) in a range of aprotic solvents (entries 2-5), dichloromethane was chosen for subsequent reactions due to its greater ability to solubilize a wide range of amine hydrochloride salts.

Table 4.1. Reaction optimization



4.1a **4.6a**

entry	solvent	base	base addition temp	yield (%)[a]	dr[b]
1	THF	triethylamine	-78 ºC	99	65:35
2	THF	triethylamine	rt	90	54:46
3	EtOAc	triethylamine	rt	77	57:43
4	Dioxane	triethylamine	rt	99	58:42
5	CH_2Cl_2	triethylamine	rt	86	60:40
6	CH_2Cl_2	Hünig's base[c]	rt	50	54:46
7	CH_2Cl_2	proton sponge[d]	rt	85	58:42
8	CH_2Cl_2	pyridine	rt	0	-

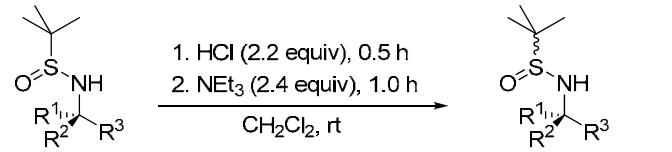
[a] Yields were determined by ^{1}H-NMR relative to 3,5-dimethoxytoluene. [b] Diastereomeric ratio was determined by NMR analysis. [c] *N*,*N*-diisopropylethyl amine. [d] 1,2-Bis(dimethylamino)naphthalene.

A variety of bases for the re-sulfinylation reaction were next evaluated. Hünig's base provided a moderate yield of the sulfinyl diastereomers (entry 6). Proton sponge provided a comparably high yield relative to triethylamine (entry 7); however, its separation from the product by simple extractive techniques was unsuccessful. As might be expected from its decreased basicity, pyridine failed to provide any product (entry 8).

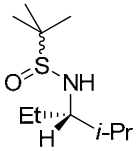
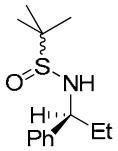
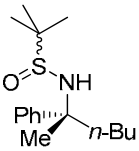
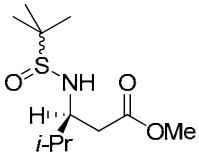
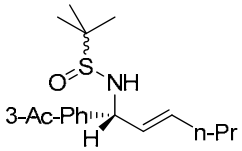
Exploration of Reaction Scope

To demonstrate the generality of the method, a variety of *N*-sulfinyl imine addition products were prepared and evaluated under the optimal reaction conditions (Table 4.2). α-Branched benzylic amines provided an approximate 3:2 ratio of *N*-sulfinyl amine diastereomers despite the structural dissimilarity of the two α-substituents (entry 2). Sterically encumbered tertiary carbinamines required slightly longer times for the deprotection of the *tert*-butanesulfinyl group (1 h versus 0.5 h), but still provided a mixture of diastereomers in high yield (entry 3). β-Amino esters (entry 4) and α-branched allylic amines (entry 5) are also competent substrates for the reaction sequence. Notably, a simple extractive isolation provided analytically pure material in all cases.

Table 4.2. Preparation of diastereomer mixtures from various *N*-*tert*-butanesulfinyl amines



diastereopure **4.1a–e** → *diastereomer mixture* **4.6a–e**

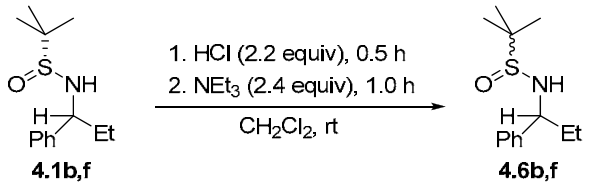
entry	diastereopure *N*-sulfinyl amine **1**	*N*-sulfinyl amine diastereomer mixture **6**		yield (%)[a]	dr
1	**4.1a** (S_S, *S*)		**4.6a**	86	60:40[b]
2	**4.1b** (R_S, *S*)		**4.6b**	98	62:38[c]
3[d]	**4.1c** (S_S, *R*)		**4.6c**	85	52:48[b]
4	**4.1d** (R_S, *S*)		**4.6d**	84	53:47[b]
5	**4.1e** (R_S, *R*)		**4.6e**	98	56:44[c]

[a] Yields were determined by mass balance of analytically pure material. [b] Diastereomeric ratio was determined by NMR analysis. [c] Diastereomeric ratio was determined by NMR and HPLC analysis. [d] The HCl-mediated *N*-*tert*-butanesulfinyl deprotection was performed for 1 h.

Mechanistic Evidence for Complete Racemization of tert-Butanesulfinyl Chloride

Diastereomerically pure *N*-sulfinyl amines generally did not provide a 1:1 mixture of diastereomers upon resulfinylation with sulfinyl chloride **4.3** (Table 4.2). This could be the result of either incomplete sulfinyl chloride racemization or dynamic resolution of the sulfinyl chloride under the reaction conditions.[6] The incomplete racemization of sulfinyl chloride was ruled out by subjecting diastereomerically pure (R_S, *S*) and (R_S, *R*) *N*-sulfinyl amines to the reaction conditions. As long as the *N*-sulfinyl amine starting material is completely deprotected and the intermediate sulfinyl chloride **4.3** fully racemizes, the same diastereomeric ratio should be obtained independent of the relative configurations of the sulfinyl and α-stereocenters. Indeed, both (R_S, *S*) and (R_S, *R*) *N*-sulfinyl amines provided a diastereomeric ratio of 62:38 (Table 4.3). As predicted, both reactions provided the same major diastereomer as opposite enantiomers: (S_S, *S*) for the (R_S, *S*) starting amine **4.1b** and (R_S, *R*) for the (R_S, *R*) starting amine **4.1f**. Therefore, the ~3:2 ratio of diastereomers is the result of dynamic resolution of sulfinyl chloride under the reaction conditions.[6]

Table 4.3. Evidence for complete racemization of sulfinyl chloride **4.3** under the reaction conditions



entry	diastereopure *N*-sulfinyl amine **4.1**		*N*-sulfinyl amine diastereomer mixture **4.6**[a]	
1	**4.1b**	(R_S, *S*)	**4.6b**	62:38 (S_S, *S*):(R_S, *S*)
2	**4.1f**	(R_S, *R*)	**4.6f**	62:38 (R_S, *R*):(S_S, *R*)

[a] Diastereomeric ratio was determined by NMR and HPLC analysis.

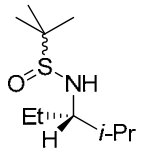
Conclusion

In conclusion, a one-pot method has been developed for the preparation of authentic diastereomers of *N*-*tert*-butanesulfinyl amines. This straightforward method, which proceeds in high yields for a broad range of *N*-sulfinyl amines, should be extremely useful for obtaining *N*-sulfinyl amine diastereomer mixtures as standards for the rapid and accurate determination of diastereomeric purity.

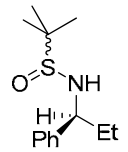
Experimental Section

General methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without purification. 1,4-Dioxane, tetrahydrofuran, and dichloromethane were dried over alumina under a N_2 atmosphere prior to use. Triethylamine, *N*,*N*-diisopropylethylamine, and pyridine were distilled under N_2 over CaH_2 immediately prior to use. All reactions were carried out in flame-dried glassware under an inert N_2 atmosphere. *N*-Sulfinyl amines **4.1a**[5], **4.1b**[5], **4.1c**[3a], **4.1d**[3b], **4.1e**[7], and **4.1f**[5] were synthesized according to the literature procedures. The ^{1}H NMR of these compounds matched the published spectra. ^{1}H and ^{13}C-NMR spectra were obtained on a Bruker AVB-400, DRX-500, AV-500, or AV-600 at room temperature. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. ^{1}H NMR and ^{13}C NMR resonances are referenced to the residual $CDCl_3$ solvent peak at 7.26 ppm and 77.23 ppm, respectively. Diastereoselectivity determinations were performed either by ^{1}H-NMR analysis or by HPLC using an Agilent 1100 series LC equipped with a silica normal phase column (Microsorb Si 100 A packing) with a multiwavelength detector. Elemental analyses and mass spectrometry analyses were performed by the University of California at Berkeley Microanalysis and Mass Spectrometry Facilities.

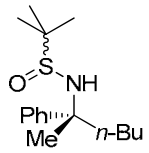
General Procedure for Preparing Authentic Mixture of *N*-*tert*-Butanesulfinyl Amines. The *N*-sulfinyl amine **4.1** (1.0 equiv) dissolved in CH_2Cl_2 (0.16 M) in an oven-dried vial equipped with a Teflon coated stir bar under nitrogen was placed in an ambient water bath. 4.4M HCl in dioxane (2.2 equiv) was added dropwise to this solution, and the reaction mixture was stirred at rt for 0.5-1 h. NEt_3 (2.4 equiv) was then added dropwise and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with EtOAc and washed successively with 1 N $NaHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide an authentic mixture of *N*-sulfinyl amine diastereomers. The extractive isolation provided analytically pure material.



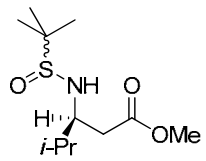
***N*-(1-Ethyl-2-methylpropyl)-*tert*-butanesulfinyl amine (4.6a).** The general procedure was followed using *N*-sulfinyl amine **4.1a** (20 mg, 0.097 mmol), 4.4 M HCl dioxane (48 μL, 0.21 mmol), and NEt_3 (32 μL, 0.23 mmol) in CH_2Cl_2 (0.61 mL) to afford 17.2 mg (86% yield) of **4.6a** as a mixture of diastereomers (60:40; S_S,*S*:R_S,*S*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by ^{1}H-NMR analysis. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.82-0.98 (m, 9H), 1.208 (s, 5.4H), 1.212 (s, 3.6H), 1.33-1.44 (m, 0.6H), 1.47-1.64 (m, 1.4H), 1.75-1.83 (m, 0.4H), 1.89-1.99 (m, 0.6H), 2.84 (d, 0.4H, J = 6.9), 2.92-2.99 (m, 1H), 3.06 (d, 0.6H, J = 6.9). The ^{1}H-NMR shifts of the (R_S,*S*) diastereomer correspond to the literature data and those of the (S_S,*S*) diastereomer correspond to the literature data for its (R_S,*R*) enantiomer.[5] MS (ESI): *m/z* 206 $[MH]^+$. Anal. Calcd for $C_{10}H_{23}NOS$: C, 58.49; H, 11.29; N, 6.82. Found: C, 58.13; H, 10.91; N, 6.50.



***N*-(1-Phenylpropyl)-*tert*-butanesulfinyl amine (4.6b).** The general procedure was followed using *N*-sulfinyl amine **4.1b** (40 mg, 0.17 mmol), 4.4M HCl dioxane (85 μL, 0.37 mmol), and NEt_3 (57 μL, 0.41 mmol) in CH_2Cl_2 (1.1 mL) to afford 39.1 mg (98% yield) of **4.6b** as a mixture of diastereomers (62:38; S_S,*S*:R_S,*S*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by both ^{1}H-NMR and HPLC analysis. HPLC analysis: (silica column, hexanes:EtOH 97:3, 1.0 mL/min, λ = 210 nm): t_{minor} = 10.6 min, t_{major} = 12.2 min. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79 (t, 1.9H, *J* = 7.3), 0.84 (t, 1.1H, *J* = 7.3), 1.18 (s, 3.4H), 1.23 (s, 5.6H), 1.71-1.91 (m, 1.4H), 2.00-2.11 (m, 0.62H), 3.41 (s, 1H), 4.25-4.32 (m, 1H), 7.24-7.38 (m, 5H). The ^{1}H-NMR shifts of the (R_S,*S*) diastereomer correspond to the literature data and those of the (S_S,*S*) diastereomer correspond to the literature data for its (R_S,*R*) enantiomer.[5] MS (ESI): *m/z* 240 $[MH]^+$. Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85. Found: C, 64.96; H, 9.07; N, 5.70.

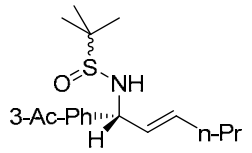


***N*-(2-Phenylhexan-2-yl)-2-methylpropanesulfinyl amine (4.6c).** The general procedure was followed using *N*-sulfinyl amine **4.1c** (20 mg, 0.071 mmol), 4.4M HCl dioxane (35 μL, 0.16 mmol), and NEt_3 (24 μL, 0.17 mmol) in CH_2Cl_2 (0.44 mL) to afford 17.0 mg (85% yield) of **4.6c** as a mixture of diastereomers (52:48; S_S,*R*:R_S,*R*). The reaction mixture was stirred for 1 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by ^{1}H-NMR analysis. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.82 (t, 1.6H, *J* =7.3), 0.83 (t, 1.4H, *J* = 1.4H), 0.94-1.36 (m, 4H), 1.21 (s, 4.7H), 1.24 (s, 4.3H), 1.72 (s, 1.6H), 1.73 (s, 1.4H), 1.84-2.04 (m, 2H), 3.46 (s, 0.48H), 3.50 (s, 0.52H), 7.20-7.29 (m, 1H), 7.337 (t, 1H, *J* = 7.6), 7.341 (t, 1H, *J* = 7.6), 7.42 (app t, 2H, *J* = 8.8). The ^{1}H-NMR shifts of the (R_S,*R*) diastereomer correspond to the literature data and those of the (S_S,*R*) diastereomer correspond to the literature data for its (R_S,*S*) enantiomer.[3a] MS (ESI): *m/z* 282 $[MH]^+$. Anal. Calcd for $C_{16}H_{27}NOS$: C, 68.28; H, 9.67; N, 4.98. Found: C, 68.65; H, 10.05; N, 4.66.

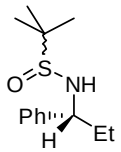


Methyl *N*-(*tert*-butanesulfinyl)-3-amino-4-methlypentanoate (4.6d). The general procedure was followed using *N*-sulfinyl amine **4.1d** (40 mg, 0.16 mmol), 4.4 M HCl in dioxane (80 μL, 0.36 mmol), and NEt_3 (54 μL, 0.38 mmol) in CH_2Cl_2 (1.0 mL) to afford 33.6 mg (84% yield) of **4.6d** as a mixture of diastereomers (53:47; R_S,*S*:S_S,*S*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was

determined by ^{1}H-NMR analysis. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (d, 1.6H, *J* = 6.8), 0.91 (d, 1.6H, *J* = 6.8), 0.94 (d, 1.4H, *J* = 6.8), 0.95 (d, 1.4H, *J* = 6.8), 1.16 (s, 4.2H), 1.20 (s, 4.8H), 1.75-1.92 (m, 0.53H), 1.93-2.08 (m, 0.47H), 2.34-2.53 (m, 0.94H), 2.61 (dd, 0.53H, *J* = 15.8, 6.2), 2.72 (dd, 0.53H, *J* = 15.8, 6.2), 3.25-3.37 (m, 0.53H), 3.42 (d, 0.47H, *J* = 8.1), 3.48-3.60 (m, 0.47H), 3.64 (s, 1.4H), 3.67 (s, 1.6H), 4.05 (d, 0.53H, 8.1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 18.1, 18.9, 19.15, 19.22, 22.8, 23.0, 32.5, 32.8, 37.8, 37.9, 51.9, 52.0, 56.20, 56.25, 59.6, 59.8, 172.5, 172.9. The ^{1}H- and ^{13}C-NMR shifts of the (R_S,*S*) diastereomer correspond to the literature data.[3b] MS (ESI): *m/z* 250 $[MH]^+$. Anal. Calcd for $C_{11}H_{23}NO_3S$: C, 52.98; H, 9.30; N, 5.62. Found: C, 53.33; H, 9.48; N, 5.30.



***N*-((*E*)-1-(3-Acetylphenyl)hex-2-enyl)-2-methylpropanesulfinyl amine (4.6e).** The general procedure was followed using *N*-sulfinyl amine **4.1e** (20 mg, 0.062 mmol), 4.4 M HCl in dioxane (31 μL, 0.14 mmol), and NEt_3 (21 μL, 0.15 mmol) in CH_2Cl_2 (0.39 mL) to afford 19.6 mg (98% yield) of **4.6e** as a mixture of diastereomers (56:44; R_S,*R*:S_S,*R*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by both ^{1}H-NMR and HPLC analysis. HPLC analysis: (silica column, hexanes:EtOH 95:5, 1.0 mL/min, λ = 222 nm): t_{minor} = 9.8 min, t_{major} = 12.7 min. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 1.3H, *J* = 7.4), 0.87 (t, 1.7H, J=7.3), 1.21 (s, 4H), 1.24 (s, 5H), 1.30–1.47 (m, 2H), 1.94–2.09 (m, 2H), 2.59 (s, 1.3H), 2.60 (s, 1.7H), 3.45 (s, 1H), 4.99 (app dt, 1H, *J* = 7.5, 2.5), 5.44–5.66 (m, 1H), 5.67–5.86 (m, 1H), 7.44 (dt, 1H, *J* = 7.7, 3.2), 7.54 (dt, 1H, *J* = 7.7, 1.3), 7.86 (d, 1H, *J* = 7.7), 7.93 (s, 0.56H), 7.94 (s, 0.44H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ 13.81, 13.83, 22.26, 22.28, 22.8, 22.9, 26.86, 26.89, 34.4, 34.5, 55.8, 56.0, 61.0, 61.1, 127.1, 127.7, 127.8, 128.0, 129.0, 129.3, 129.9, 131.1, 132.1, 132.7, 134.5, 135.2, 137.7, 137.9, 142.3, 143.2, 198.0. The ^{1}H- and ^{13}C-NMR shifts of the (R_S,*R*) diastereomer correspond to the literature data.[7] (ESI): *m/z* 322 $[MH]^+$. Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.37; H, 8.56; N, 4.11.



***N*-(1-Phenylpropyl)-*tert*-butanesulfinyl amine (4.6f).** The general procedure was followed using *N*-sulfinyl amine **4.1f** (40 mg, 0.17 mmol), 4.4M HCl dioxane (85 μL, 0.37 mmol), and NEt_3 (57 μL, 0.41 mmol) in CH_2Cl_2 (1.1 mL) to afford 37.4 mg (93% yield) of **4.6b** as a mixture of diastereomers (62:38; R_S,*R*:S_S,*R*). The reaction mixture was stirred for 0.5 h after the HCl addition and for 1 h after the NEt_3 addition. The diastereomeric ratio was determined by both ^{1}H-NMR and HPLC analysis. HPLC analysis: (silica column, hexanes:EtOH 97:3, 1.0 mL/min, λ = 210 nm): t_{minor} = 10.2 min, t_{major} = 11.7 min. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79 (t, 1.9H, *J* = 7.5), 0.84 (t, 1.1H), *J* = 7.5), 1.18 (s, 3.4H), 1.23 (s, 5.6H), 1.71-1.89 (m, 1.4H), 2.02-2.11 (m, 0.62H), 3.39 (s, 1H), 4.25-4.32 (m, 1H), 7.26-7.37 (m, 5H). The ^{1}H-NMR shifts of

the (R_S,R) diastereomer correspond to the literature data and those of the (S_S,R) diastereomer correspond to the literature data for its (R_S,S) enantiomer.[5] MS (ESI): *m/z* 240 $[MH]^+$. Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85. Found: C, 65.27; H, 9.02; N, 5.71.

References

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Chapter 5. Total Synthesis and Chemistry of (–)-Aurantioclavine.

The concise total synthesis of (–)-aurantioclavine has been achieved by taking advantage of strategies for the asymmetric alkenylation of N-tert-butanesulfinyl imines. The enantiomerically pure natural product was prepared in 6 steps and 27% overall yield by using the Rh-catalyzed addition of a MIDA boronate and in 5 steps and 29% yield by employing a Grignard reagent addition sequence. The majority of this work was published in a communication (Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, submitted).

Based on a biosynthetic proposal, a preliminary exploration of (–)-aurantioclavine's role as an intermediate en route to the complex polyclic alkaloids of the communesin family was also carried out. Initial work towards the asymmetric synthesis of communesin F established that the coupling of a derivative of (–)-aurantioclavine and a quinone methide imine derivative of tryptamine is a feasible transformation.

Introduction

(–)-Aurantioclavine ((–)-**5.1**) was isolated from *Penicillium aurantiovirens* in 1981,[1] and soon after its discovery, concise syntheses of racemic aurantioclavine were reported in the literature.[2] This ergot alkaloid continues to attract considerable interest from the synthetic community due to its proposed role as an intermediate in the biosynthesis of the complex polycyclic alkaloids of the communesin family (Figure 5.1).[3] However, despite this attention, the asymmetric synthesis of aurantioclavine has only recently been accomplished in 13 steps and <1% overall yield from commercially available material.[4] The stereocenter was successfully set via a Pd(II)-catalyzed oxidative kinetic resolution of an alcohol. Herein, we report a new, highly efficient synthesis of (–)-aurantioclavine that utilizes asymmetric alkenylation of a densely functionalized *N*-*tert*-butanesulfinyl imine.

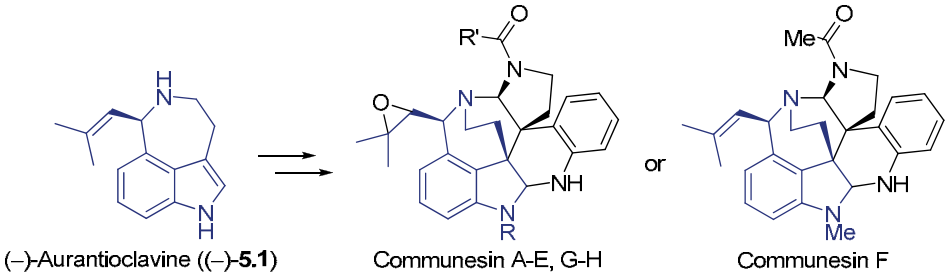


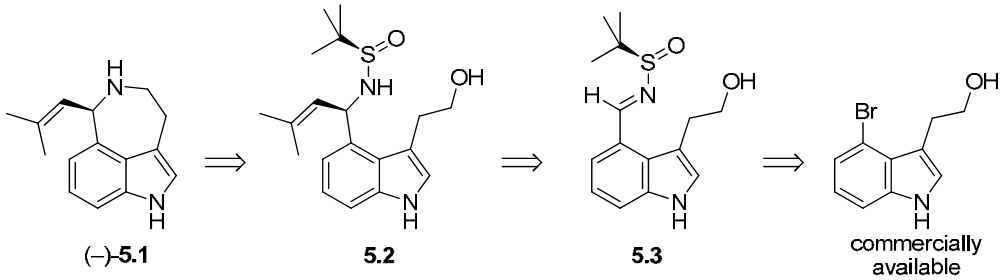
Figure 5.1. (–)-Aurantioclavine as an intermediate en route to the communesins.

Total Synthesis of (–)-Aurantioclavine

Retrosynthetic Analysis

Our approach to (–)-aurantioclavine is depicted in Scheme 5.1. We envisioned that the natural product could be accessed from sulfinamide **5.2** via cyclization to form the azepine ring followed by cleavage of the sulfinyl group. The asymmetric synthesis of sulfinamide **5.2** would be accomplished by the addition of the appropriate organometallic reagent to *N*-sulfinyl imine **5.3**.[5] This imine could in turn be generated by the condensation of *N*-*tert*-butanesulfinamide with the aldehyde resulting from formylation of 4-bromo-tryptophol.[6]

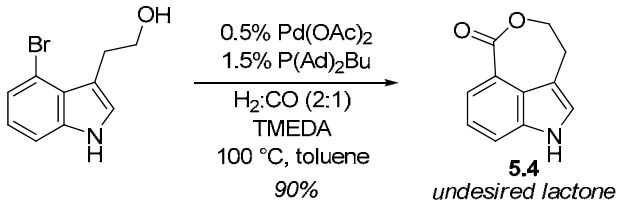
Scheme 5.1. Retrosynthetic analysis of (–)-aurantioclavine



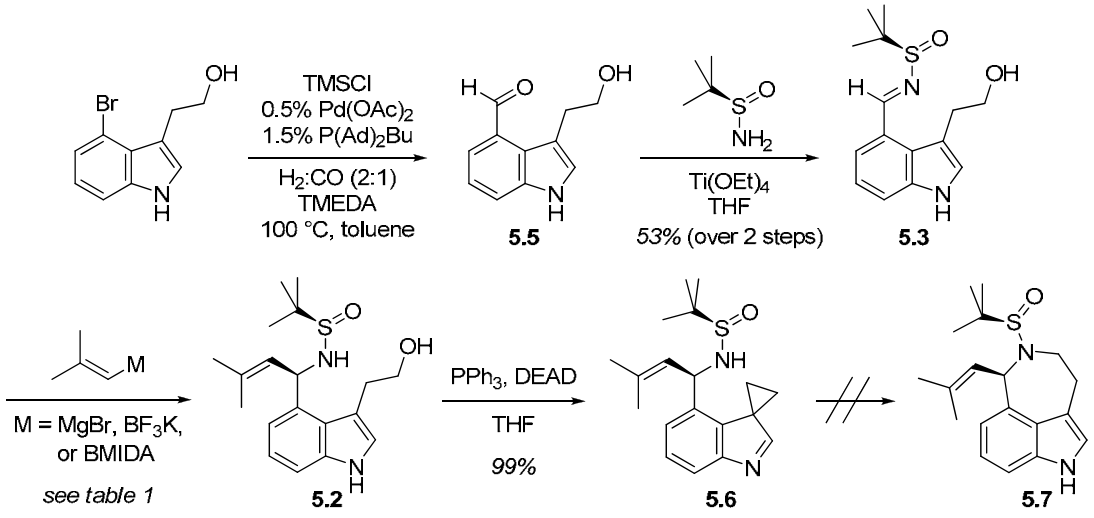
Initial Approach Toward (–)-Aurantioclavine Synthesis

Installation of the formyl group was initially attempted via a traditional approach involving KH-mediated deprotonation of the acidic sites, followed by a lithiation-formylation sequence with *t*BuLi and DMF.[7] While the desired aldehyde could be obtained using this method, the reaction yield was highly variable due to the poor solubility of the initially formed dianion. We next turned to the highly efficient Pd-catalyzed formylation of aryl and heteroaryl bromides reported by Beller and coworkers.[8] While application of their general procedure resulted in complete conversion to undesired lactone **5.4** (Scheme 5.2), in situ protection of the alcohol with TMSCl prevented this cyclization and afforded the desired aldehyde **5.5** (Scheme 5.3). Isolation of aldehyde **5.5** was complicated by polymerization via intermolecular hemiacetal formation, and therefore the unpurified material was directly converted to *N*-*tert*-butanesulfinyl imine **5.3** in 53% yield over the two steps. If the aldehyde is instead isolated (41% yield), formation of *N*-*tert*-butanesulfinyl imine **5.3** proceeds in 84% yield.

Scheme 5.2.



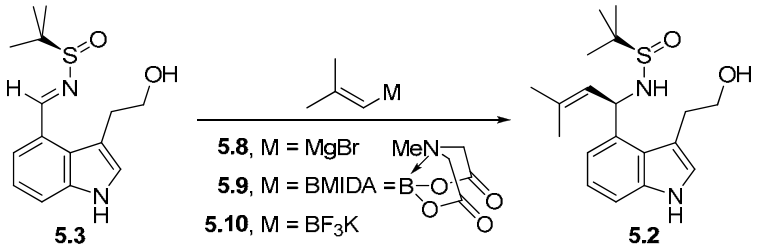
Scheme 5.3. Initial route towards the synthesis of aurantioclavine ((–)-**5.1**)



With the substrate for the key reaction in hand, we explored the alkenylation of *N*-sulfinyl imine **5.3** (Table 5.1). Addition of Grignard reagent **5.8** as a solution in ether, resulted in precipitation of the dianion and no desired product (entry 1). When a solution of the Grignard reagent in THF was employed, the reaction proceeded in good yield but with poor diastereoselectivity (entry 2). We recently developed a method for the rhodium-catalyzed

addition of alkenyltrifluoroborates[9] and *N*-methyliminodiacetic acid (MIDA) boronates[10] to *N*-*tert*-butanesulfinyl imines. Consistent with the higher diastereoselectivity previously observed in the addition of alkenylboron reagents, the additions of both MIDA boronate **9** (entry 3) and trifluoroborate **5.10** (entry 4) proceeded in moderate yields and with high diastereoselectivities. Taking advantage of the hydrolytic stability of the *N*-sulfinyl imine, higher yields could be attained by adding the trifluoroborate in three portions (entry 5). Significantly, the synthesis of sulfinamide **5.2** was achieved in high yield and selectivity without requiring protection of the alcohol or indole moieties.

Table 5.1. Alkenylation of *N*-sulfinyl imine **3** with various organometallic reagents



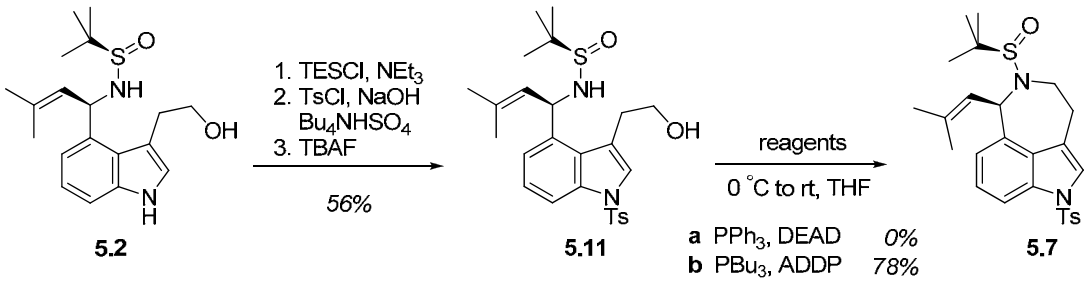
entry	M (equiv)	yield (%)[a]	conversion (%)[a]	dr[b]
1[c]	MgBr in Et_2O (3.5 equiv)	0	38	-
2[c]	MgBr in THF (3.5 equiv)	69	89	33:67
3[d]	BMIDA (2 equiv)	23	50	97:3
4[e]	BF_3K (2 equiv)	42	64	97:3
5[e]	BF_3K (3 x 1.5 equiv)	84 (81)[f]	94	97:3

[a] Yield and conversion were determined by ^{1}H NMR relative to an external standard. [b] Diastereoselectivity was determined by HPLC comparison to authentic diastereomers. [c] Reaction was run in CH_2Cl_2.[16] [d] Reaction was performed using $[Rh(OH)(cod)]_2$, dppbenz, and K_3PO_4 in H_2O/dioxane.[10] [e] Reaction was performed using $[Rh(OH)(cod)]_2$, dppbenz, and NEt_3 in H_2O/DMF.[9] [f] Isolated yield of diastereomerically pure material.

The next step en route to the synthesis of (–)-aurantioclavine was cyclization to provide the azepine ring. We decided to use the Mitsunobu reaction for this cyclization because this approach has been used successfully for the formation of 5-membered rings with *N*-*tert*-butanesulfinamides and primary alcohols.[11] To our surprise, Mitsunobu reaction of alcohol **5.2** resulted in formation of spiro[cyclopropyl]indolenine **5.6**[12] (Scheme 5.3). A variety of acidic conditions were explored for ring expansion of indolenine **5.6** to azepine **5.7**. Unfortunately, decomposition was observed both with Brønsted acids (HCl, TFA) and Lewis acids (BF_3OEt_2, $Yb(OTf)_2$, $AuCl_3$), and upon treatment with Schreiner's thiourea catalyst,[13] the indole-thiourea adduct was instead isolated. Furthermore, indolenine **5.6** was unreactive under basic conditions. When the sulfinamide moiety was deprotonated with KH, no reaction was observed.

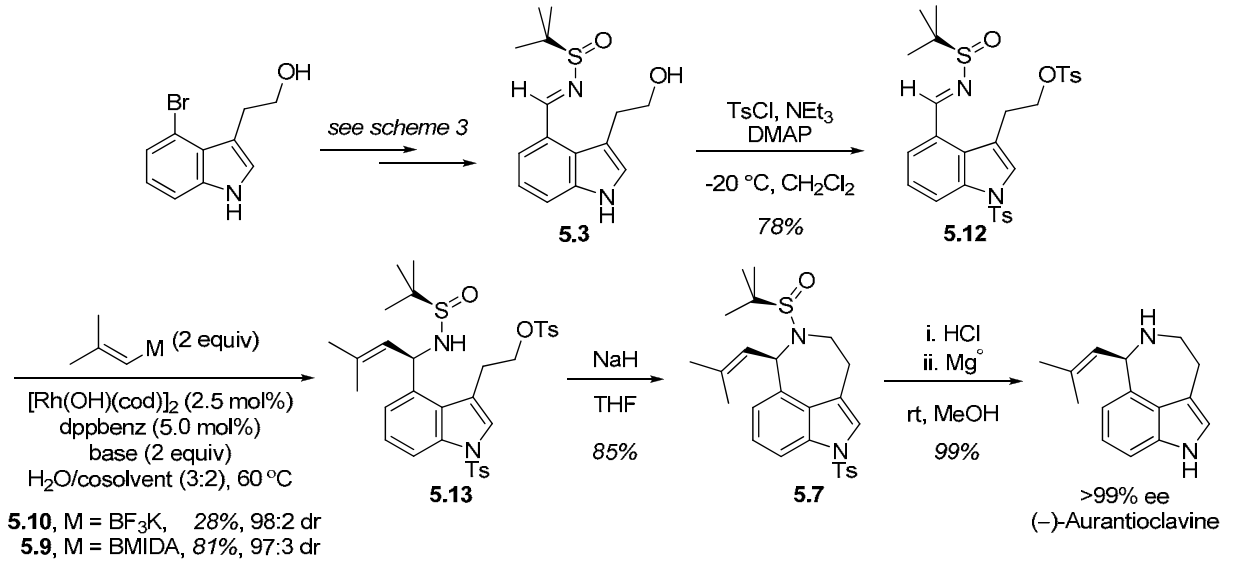
The inability to carry forward spiro-indolenine **5.6**, required us to revise our strategy. We hypothesized that cyclization without formation of the undesired indolenine would require deactivation of the indole moiety of **5.2**. Selective tosylation of the indole was accomplished via a three-step Meienhofer-type[14] procedure (Scheme 5.4). Mitsunobu reaction of alcohol **5.11** using the standard reagents,[11] diethyl azodicarboxylate (DEAD) and triphenylphosphine, resulted in no reaction. For weakly acidic nucleophiles, conditions have been developed using the more basic 1,1'-(azodicarbonyl)dipiperidine (ADDP) and more nucleophilic tributylphosphine.[15] Upon switching to these more reactive reagents, azepine **5.7** was cleanly formed in good yield. While this approach was successful, selective protection of the indole moiety of **5.2** was inefficient because it required protecting group manipulations of the more nucleophilic alcohol. A much more appealing strategy was tosylation of both the indole and alcohol, which would deactivate the indole while simultaneously activating the alcohol for a subsequent S_N2-mediated cyclization. Bis-tosylation of *N*-sulfinyl allylic amine **5.2** was met with limited success. Careful evaluation of the reaction products suggested that the sulfinamide moiety was unstable under these conditions. Fortunately, tosylation of the *N*-sulfinyl imine precursor (**5.3**) proceeded in good yield as long as the reaction solution was maintained at low temperature (Scheme 5.5).

Scheme 5.4. Selective tosylation and Mitsunobu reaction of indole **5.2**



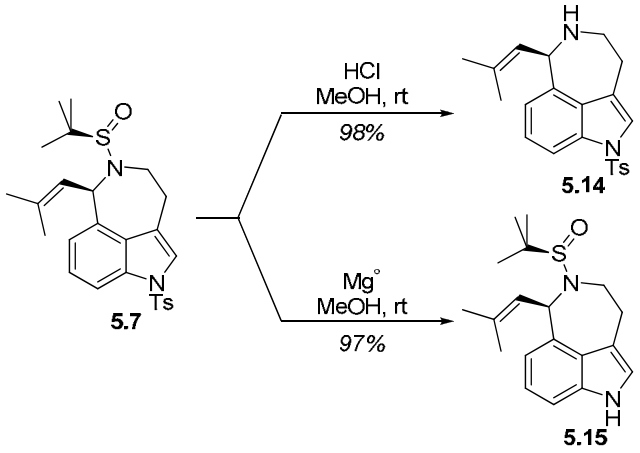
While the Rh(I)-catalyzed addition of trifluoroborate **5.10** to bis-tosylated *N*-sulfinyl imine **5.12** was not very efficient, the newly developed MIDA boronate slow release conditions[10] provided sulfinamide **5.13** in high yield and diastereoselectivity (Scheme 5). After chromatography, diastereomerically pure **5.13** was isolated in 78% yield. Furthermore, cyclization of sulfinamide **5.13** proceeded smoothly upon deprotonation with NaH.

Scheme 5.5. Total synthesis of (–)-aurantioclavine via the Rh-catalyzed addition of MIDA boronate **5.9**



To complete the synthesis, only the removal of the sulfinamide and tosyl groups remained. Initial attempts to remove both of the protecting groups with a single reagent were unsuccessful. Treatment with MeLi or TBAF resulted in deprotection of the tosyl group as well as multiple other side products. Magnesium in methanol proved to be a mild and highly effective method for deprotection of the tosyl group. Additionally, acidic alcoholysis with HCl in methanol, the general conditions for removing *tert*-butanesulfinyl groups,[16] resulted in quantitative deprotection of the sulfinyl group (Scheme 5.6). These straightforward deprotections could be carried out separately, in either order, or in one-pot. The ability to selectively deprotect either functional group provides great flexibility for subsequent synthetic approaches to the communesins, and the one-pot double-deprotection resulted in the formation of (–)-aurantioclavine in quantitative yield (Scheme 5.5).

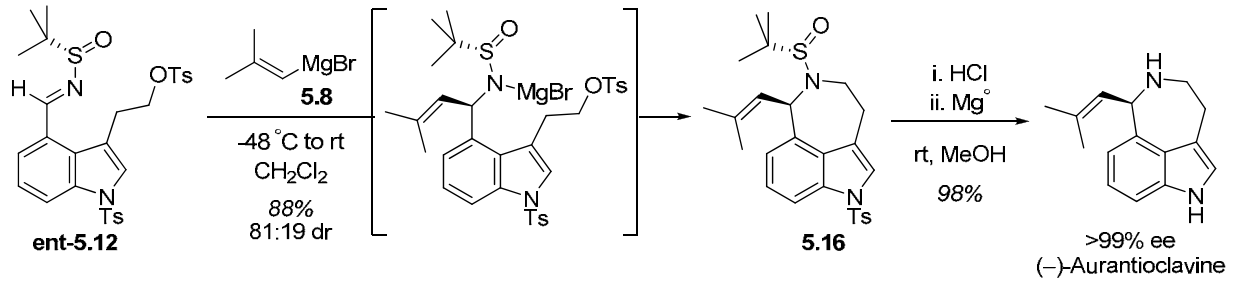
Scheme 5.6. Selective deprotection of tosyl and sulfinyl groups



Synthesis of (–)-Aurantioclavine by employing a Grignard Reagent Addition Sequence

Despite the precedence for lower selectivity, we realized that Grignard reagent addition could prove more efficient than the addition of boron reagents if spontaneous cyclization occurred upon formation of the nucleophilic sulfinamide anion (Scheme 5.7).[17] The solvent of the Grignard solution was again found to be critical to reaction success, with no cyclization observed in ether. However, addition of Grignard **5.8** as a solution in the more highly coordinating solvent THF cleanly afforded cyclized product **5.16** with moderate diastereoselectivity. After chromatography, diastereomerically pure product was isolated in 72% yield. It is noteworthy that because Grignard addition provides the opposite diastereoselectivity to that for the Rh-catalyzed addition of the MIDA boronate, both *N*-*tert*-butanesulfinyl azepine diastereomers **5.7** and **5.16** are accessible. The one-pot double-deprotection conditions were equally successful for azepine diastereomer **5.16**, providing (–)-aurantioclavine in high yield.

Scheme 5.7. Total synthesis of (–)-aurantioclavine via the addition of Grignard reagent **5.8**

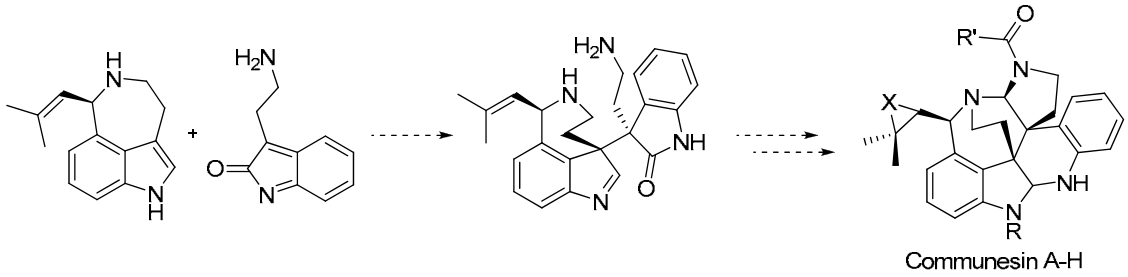


Evaluating (–)-Aurantioclavine as an Intermediate en Route to the Communesins

Biosynthetic Proposal

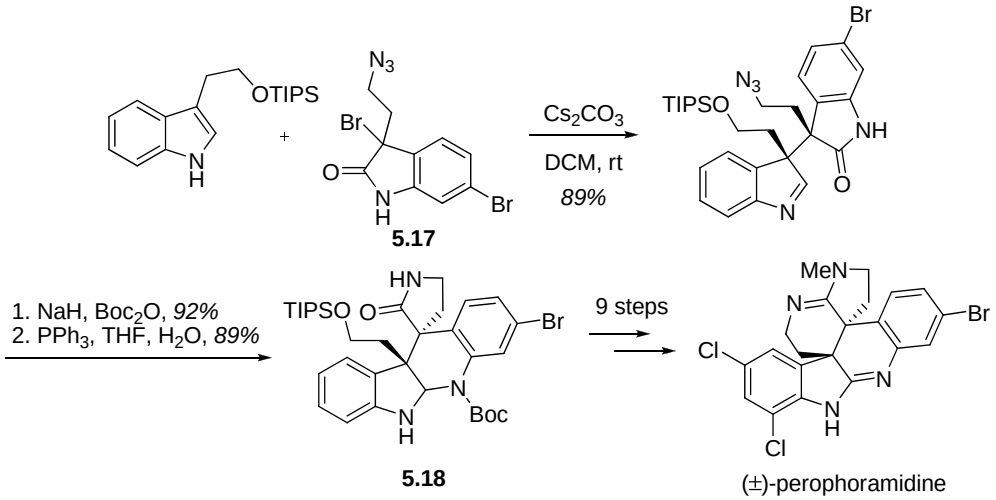
The polycyclic framework and vicinal quaternary stereocenters of communesins A-H (Figure 5.1) have attracted intensive synthetic efforts.[3c] The first successful synthesis of a member of this indole alkaloid family, (±)-communesin F, was recently accomplished by Qin and coworkers in 23 reaction steps and about 3% overall yield.[18] As a means toward the asymmetric synthesis of members of the communesin family, Stoltz and coworkers have proposed a biosynthetic approach that involves coupling of (–)-aurantioclavine with a quinone methide imine derivative of tryptamine (Scheme 5.8).[3] Because our succinct synthesis provides rapid access to significant quantities of (–)-aurantioclavine, we decided to evaluate the proposed biomimetic approach for the asymmetric synthesis of communesin F.

Scheme 5.8. Biosynthetic proposal for the synthesis of the communesins



Funk and coworkers have carried out the total synthesis of (±)-perophoramidine, a natural product class closely related to the communesins, using a synthetic approach similar to the biosynthesis proposed for the communesins.[19] Coupling of 3-(2-triisopropylsilyloxyethyl)indole and oxindole **5.17** proceeded smoothly with 95:5 endo:exo selectivity when cesium carbonate was used as the base (Scheme 5.9). Subsequent cyclization onto the *N*-Boc-imide upon reduction of the azido functionality delivered aminal **5.18**, which was taken onto the natural product in nine steps. Unlike perophoramidine, the vicinal quaternary carbon centers of the communesins possess a *cis* relationship. While this raises a concern as to whether this strategy will be applicable to the synthesis of the communesins, the additional carbocycle of aurantioclavine could certainly bias the system towards the desired pathway.

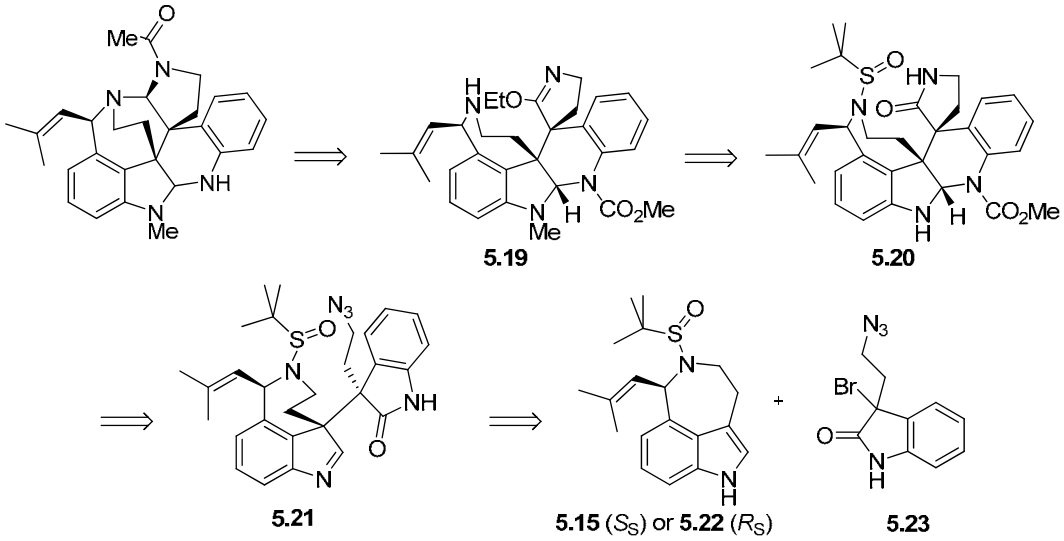
Scheme 5.9. Total synthesis of (±)-perophoramidine by Funk and coworkers



Retrosynthetic Analysis

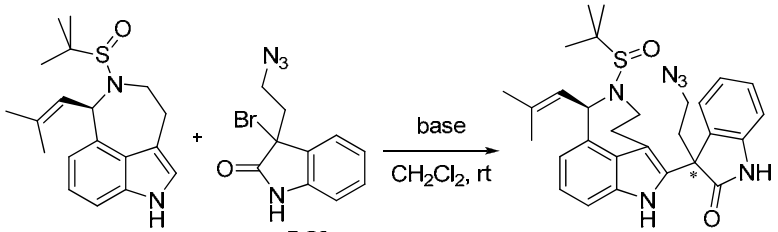
Our approach to (–)-communesin F is depicted in Scheme 5.10. Aminal **5.19** is an intermediate in Qin's synthesis of (±)-communesin F, and would therefore constitute a formal synthesis. We envisioned that aminal **5.19** could be prepared from aminal **5.20** via imidate formation, methylation of the indole, and cleavage of the *N*-sulfinyl group. The synthesis of aminal **5.20** could be accomplished by the same amide activation, azide reduction/cyclization reaction sequence used by Funk in the synthesis of perophoramidine. Indolenine **5.21** could in turn potentially be generated by coupling of oxindole **5.23** with either azepine diastereomer **5.15** or **5.22**.

Scheme 5.10. Retrosynthetic analysis of (–)-communesin F



The coupling of both azepine diastereomers **5.15** and **5.22** with oxindole **5.23** proceeded in good yield. Interestingly, the diastereoselectivity was strongly affected by both the stereochemistry of the sulfinyl group and the choice of base (Table 5.2). The highest selectivity was observed with cesium carbonate and azepine **5.15**. By cleaving the sulfinyl groups, it was confirmed that both azepines favored formation of the same stereochemistry at the newly formed quaternary center (the absolute configuration of the newly formed stereocenter is (*S*) as determined by X-ray analysis, vide infra). Notably, the ^{1}H and ^{13}C NMR data for both products **5.24** and **5.25** (Table 5.2) are consistent with rearomatization of the indole ring via 3,2-migration from an initially formed 3,3-substituted indolenine, e.g., **5.21** (Scheme 5.10).

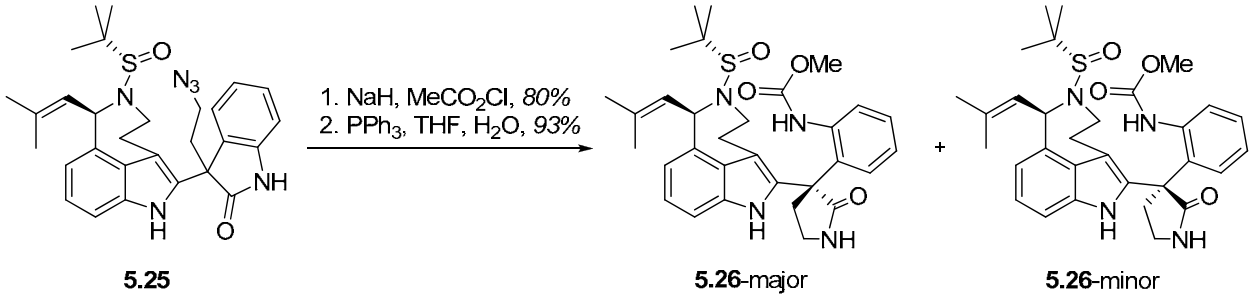
Table 5.2. Diastereoselectivity observed for the coupling of **5.23** and **5.15** or **5.22** with various bases



entry	base	azepine **5.24** (from **5.15**)	azepine **5.25** (from **5.22**)
1	Cs_2CO_3	85:15 (*S*:*R*)	55:45 (*S*:*R*)
2	NEt_3	66:33 (*S*:*R*)	76:24 (*S*:*R*)

To rigorously confirm the structures of **5.24** and **5.25** as well as establish the stereochemistry of the newly formed stereocenter in each product, X-ray structural analysis was desired. However, these azepine compounds were not stable for prolonged periods of time at room temperature, and therefore each was further functionalized. The amide activation and azide reduction/cyclization cascade both proceeded cleanly to afford indole **5.26** in high yield (Scheme 5.11). The diastereomers of **5.26** were successfully separated by chromatography, and the stereochemistry and structure of the major diastereomer was established by single X-ray diffraction to confirm that a 3,2-migration occurred had indeed occurred.

Scheme 5.11. Pyrrolidinone formation



To define the stage at which 2,3-migration occurs, the coupling reaction of **5.23** and **5.15** was performed in an NMR tube with monitoring by ^{13}C NMR analysis for the appearance of the diagnostic indolenine peak around 175 ppm. In this way we were able to confirm that the migration either occurs very rapidly at room temperature or the alkylation reaction occurs directly at the 2-position. Future experiments will involve exploration of other derivatives of azepine **5.15** or **5.22** and other reaction conditions for the coupling reaction. For example, treatment with a stronger base such as NaH would deprotonate the indole prior to the addition and avoid formation of an iminium-type intermediate, which could in turn prevent the 3,2-migration from occurring.

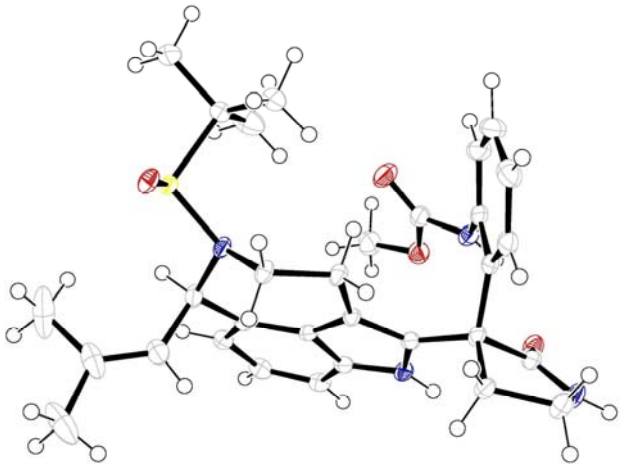


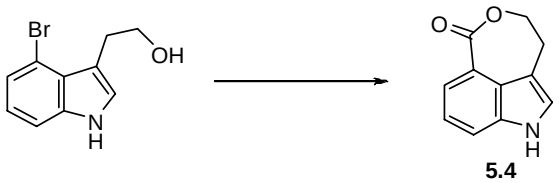
Figure 5.2. X-ray crystal structure of **5.26**-major with thermal ellipsoids drawn at the 50% probability level.

Conclusion

The asymmetric total synthesis of (–)-aurantioclavine has been accomplished in 6 steps and 27% overall yield by using a MIDA boronate and in 5 steps and 29% overall yield by using a Grignard reagent. The syntheses are considerably shorter and higher yielding than the previously reported synthesis[4] and provide rapid access to significant quantities of (–)-aurantioclavine. This work also highlights the synthetic utility of the various methodologies for the alkenylation of *N*-*tert*-butanesulfinyl imines. Additionally, a preliminary attempt at a biomimetic asymmetric synthesis of communesin F was unsuccessful, but revealed that coupling of (–)-aurantioclavine and a quinone methide imine derivative of tryptamine is a viable transformation.

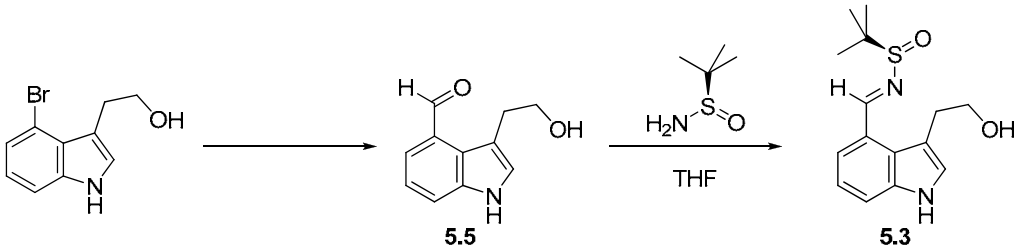
Experimental Section

General methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without purification. 1,4-Dioxane, tetrahydrofuran, diethyl ether, methylene chloride, and toluene were obtained from a Seca Solvent Systems by GlassContour (solvent dried over alumina under an N_2 atmosphere). Methanol and triethylamine were distilled under N_2 over CaH_2 immediately prior to use. Anhydrous *N*,*N*-dimethylformamide (water <50 ppm) was purchased from Acros. All liquids and reagents were thoroughly degassed using three freeze-pump-thaw cycles prior to introduction to the inert atmosphere box. (*S*)- and (*R*)-*tert*-butanesulfinamide were provided by AllyChem Co. Ltd (Dalian, China). 2,2-Dimethylethenyl MIDA boronate (**5.9**) was synthesized according to literature procedure.[10] All reactions were carried out in flame-dried glassware under an inert N_2 atmostphere. Flash column chromatography was carried out either with Merck 60 230-240 mesh silica gel, or using a Biotage SP Flash Purification System (Biotage No. SP1-B1A) with Flash+ 3 cartridges (Biotage No. FPK0-1107-16046). Diastereoselectivity determinations were performed using an Agilent 1100 series LC equipped with a silica normal phase column (Microsorb Si 100 A packing) with a multiwavelength detector. ^{1}H and ^{13}C-NMR spectra were obtained on a Bruker AVB-400, DRX-500, AV-500, or AV-600 at room temperature. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. ^{1}H NMR resonances are referenced to either the residual solvent peak ($CDCl_3$, 7.26 ppm; acetone-d_6, 2.05 ppm) or TMS (0.00 ppm) and ^{13}C NMR resonances are referenced to the residual solvent peak ($CDCl_3$, 77.23 ppm; acetone-d_6, 29.84 ppm). IR spectra were recorded on a Nicolet Avatar 350 FTIR spectrometer equipped with an attenuated total reflectance accessory and only partial data are listed. Melting points were determined on a Laboratory Devices Mel-Temp 3.0 and are reported uncorrected. Elemental analyses and mass spectrometry analyses were performed by the University of California at Berkeley Microanalysis and Mass Spectrometry Facilities.



5.4

Lactone 5.4. In an inert atmosphere box, a 100-mL Fisher-Porter-Bottle (a high pressure reaction vessel) was charged with $Pd(OAc)_2$ (2.3 mg, 0.010 mmol), cataCXium A (10.8 mg, 0.0300 mmol), and toluene (3 mL). TMEDA (0.225 mL, 1.50 mmol) and 4-bromotryptophol[18] (480 mg, 2.00 mmol) were then added. The reaction vessel was removed from the inert atmosphere box, and the reaction mixture was purged with synthesis gas by pressurizing with 5 bar H_2/CO (2:1) and evacuating three times. After 21 h at a pressure of 5 bar (refilled as necessary) and 100 ºC, the reaction mixture was cooled to room temperature and diluted with saturated aqueous $NaHCO_3$. The aqueous layer was then washed with EtOAc (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (40-60% EtOAc/hexanes) afforded 335 mg (90%) of **5.4** as a pale yellow solid. ^{1}H NMR (500 MHz, acetone-d_6): δ 3.20 (t, 2H, J = 5.0), 4.61 (t, 2H, J = 5.0), 7.26 (t, 1H, J = 8.0), 7.38 (s, 1H), 7.70 (d, 1H, J = 8.0), 7.85 (d, 1H, J = 7.2), 10.50 (br s, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ 28.4, 70.3, 114.8, 117.5, 121.6, 122.2, 124.7, 126.1, 126.8, 138.0, 170.6. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{11}H_{10}NO_2$, 188.0706; found, 188.0711.

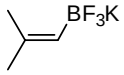


5.5 **5.3**

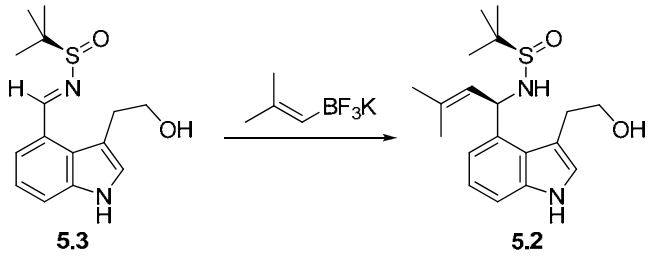
(*R*)-*N*-*tert*-Butanesulfinyl aldimine 5.3. The preparation of 4-formyltryptophol was adapted from Beller's general procedure for hydroformylation.[8] In an inert atmosphere box, a 100-mL Fisher-Porter-Bottle (high pressure reaction vessel) was charged with 4-bromotryptophol[18] (480 mg, 2.00 mmol), *N*,*N*,'*N*,'*N*-tetramethylethylenediamine (0.225 mL, 1.50 mmol), and toluene (2 mL). TMSCl (0.266 mL, 2.10 mmol) was added dropwise, and the reaction mixture was stirred for several minutes. In the mean time, cataCXium A (10.8 mg, 0.0300 mmol) was dissolved in toluene (1 mL) and added to a vial containing $Pd(OAc)_2$ (2.3 mg, 0.001 mmol). *N*,*N*,'*N*,'*N*-Tetramethylethylenediamine (0.225 mL, 1.50 mmol) was added to the resulting catalyst and ligand mixture which was subsequently added to the Fisher-Porter-Bottle. The reaction vessel was removed from the inert atmosphere box, and purged with synthesis gas by pressurizing with 5 bar H_2/CO (2:1) and evacuating three times. After 18 h at a pressure of 5 bar (refilled as necessary) and 100 ºC, the reaction mixture was cooled to room temperature. THF (3 mL) and 3 M HCl (3 mL) were added to the reaction mixture. After stirring for 30 min, the reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford aldehyde **5.5** as a bright yellow oil. Aldehyde **5.5**, which is unstable, was taken on without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (t, 2H, J = 6.4), 3.90 (t, 2H, J = 6.4), 7.27 (d, 1H, J = 2.4), 7.32 (t, 1H, J = 7.6), 7.63 (d, 1H, J = 8.0), 7.70 (d, 1H, J = 7.2),

8.49 (br s, 1H), 10.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.7, 63.9, 114.2, 118.2, 121.4, 125.2, 127.1, 128.2, 130.3, 138.2, 193.6. MS (ESI): *m/z* 190 $[MH]^+$.

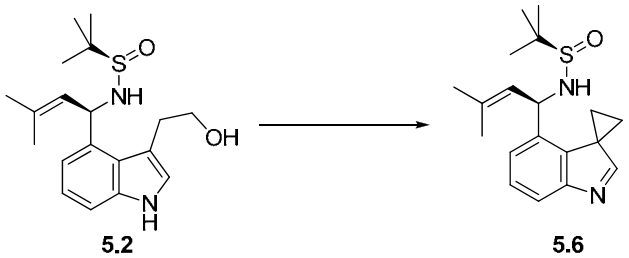
A 0.5 M solution of the crude 4-formyltryptophol and $Ti(OEt)_4$ (0.84 mL, 4.0 mmol) was prepared in THF (4 mL) under a N_2 atmosphere. Then, (*R*)-*tert*-butanesulfinamide (267 mg, 2.20 mmol) was added. The reaction solution was stirred overnight at room temperature. While rapidly stirring, the reaction was quenched by adding an equal volume of brine (4 mL). The mixture was diluted with EtOAc (10 mL) and stirred vigorously for 20 min. The resulting mixture was filtered through a pad of Celite, which was washed thoroughly with EtOAc (200 mL). The filtrate was transferred to a separatory funnel and washed with brine. The brine was then washed with a small amount of EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 40-100% EtOAc/hexanes) afforded 310 mg (53%, 2 steps) of **5.3** as a bright yellow solid. mp 129.5-130.5 ºC. $[\alpha]_D^{23}$ −278.0º (*c* 1.0, $CHCl_3$). IR 3252, 2899, 1572, 1351, 1269, 1039 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (s, 9H), 3.18 (t, 2H, *J* = 7.0), 3.31 (br t, 1H, *J* = 6.2), 3.83 (app q, 2H, *J* = 6.4), 7.13 (d, 1H, *J* = 2.5), 7.21 (t, 1H, *J* = 8.0), 7.49 (d, 1H, *J* = 8.0), 7.87 (d, 1H, *J* = 7.5), 9.13 (br s, 1H), 9.30 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.7, 32.0, 58.1, 62.6, 112.3, 116.0, 120.2, 121.8, 126.3, 126.7, 126.8, 138.1, 162.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{15}H_{21}N_2O_2S$, 293.1318; found, 293.1325.



Potassium 2,2-dimethylethenyltrifluoroborate (5.10). To a 5.8 M solution of trimethylborate (0.75 mL, 6.6 mmol) in THF (1.1 mL) cooled to -78 ºC, was added 2-methyl-1-propenylmagnesium bromide (11 mL, 0.5 M in THF, 5.5 mmol) over 30 min using an addition funnel. The reaction mixture was stirred at -78 ºC for 15 min and then warmed to room temperature with stirring for 1 h. After cooling the reaction mixture to 0 ºC, a 30% aqueous HCl solution (8.2 mL) was added, and the mixture was stirred for 1 h at 0 ºC and then 30 min at room temperature. The reaction mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and concentrated under reduced pressure to ~ 5 mL. To avoid decomposition of the boronic acid, it is important to avoid concentrating to dryness. MeOH (1.5 mL) was added and the solution was concentrated under reduced pressure to ~ 2 mL. The solution of boronic acid was cooled to 0 ºC, and a 4.5 M solution of KHF_2 (1.51 g, 19.3 mmol) in water was added dropwise. The reaction mixture was stirred for 1 h at 0 ºC. After removing the water by lyophilization, the dried solids were triturated with hot acetone (100 mL), and filtered to remove inorganic salts. The resulting filtrate was concentrated and redissolved with heating in a minimal amount of acetone (35 mL). Addition of Et_2O (10 mL) and filtration of the precipitate, afforded 564 mg (63%) of **5.10** as a white solid. Spectral data corresponded to previously reported data.[9]

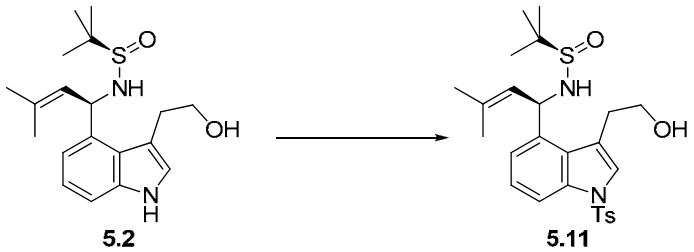


(R_S, *R*)-*N*-*tert*-Butanesulfinamide 5.2. In an inert atmosphere box, hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (7.8 mg, 0.017 mmol) was dissolved in DMF (1.05 mL) and added to a pressure tube containing 1,2-bis(diphenylphosphino)benzene (15.2 mg, 0.034 mmol). The resulting mixture of catalyst and ligand was added to a 20-mL pressure tube containing a stirbar and trifluoroborate **5.10** (166 mg, 1.02 mmol). To the mixture of catalyst, ligand, and trifluoroborate was added aldimine **5.3** (200 mg, 0.680 mmol) dissolved in DMF (1.05 mL), followed by water (3.3 mL), and triethylamine (0.189 mL, 1.36 mmol). The pressure tube was capped, heated to 60 °C, and stirred for 1 h. Additional trifluoroborate **5.10** (166 mg, 1.02 mmol) was added twice with stirring at 60 °C for 1 h in between the additions. After the last addition, the reaction mixture was heated to 60 °C and stirred for another 1.5 h. The reaction mixture was cooled to room temperature, diluted with water (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product (97:3 dr). Column chromatography (Biotage Flash+ cartridge, 70-100% EtOAc/hexanes) afforded 193 mg (81%, >99:1 dr) of **5.2** as an off-white solid. An authentic mixture of *N*-sulfinyl amine diastereomers for diastereoselectivity determination was prepared by the addition of 2-methyl-1-propenylmagnesium bromide to (R_S)-sulfinyl imine **5.3** (69%, 33:67 dr) according to the general literature procedure for Grignard reagent additions to *N*-*tert*-butanesulfinyl imines.[20] HPLC (silica column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{major} = 17.8 min, t_{minor} = 21.7 min.) mp 124.7-126.0 ºC. IR 3232, 2919, 1439, 1364, 1287, 1048, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.78 (s, 6H), 3.15-3.20 (m, 1H), 3.26-3.32 (m, 1H), 3.67-3.71 (m, 1H), 3.73 (s, 1H), 3.89-3.93 (m, 1H), 4.03 (br s, 1H), 5.58 (d, 1H, *J* = 8.5), 5.98 (d, 1H, *J* = 8.5), 6.94 (d, 1H, *J* = 1.5), 7.14 (t, 1H, *J* = 7.5), 7.22 (d, 1H, *J* = 7.5), 7.25 (d, 1H, *J* = 7.5), 8.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.1, 22.8, 26.2, 31.5, 51.1, 55.6, 64.4, 111.4, 112.5, 119.2, 122.0, 124.4, 124.6, 125.5, 134.7, 136.4, 137.6. HRMS-ESI (m/z): $[MNa]^+$ calcd for $C_{19}H_{28}N_2O_2SNa$, 371.1764; found, 371.1774.

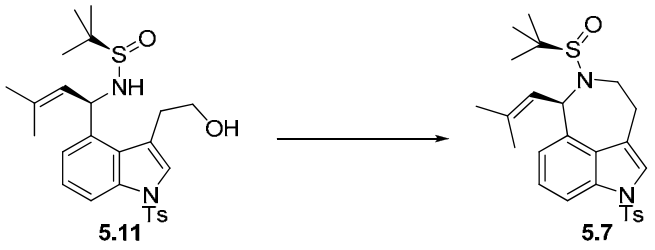


(R_S, *R*)-Spiro[cyclopropane-1,3'-indolenine] (5.6). To a 0.1 M solution of sulfinamide **5.2** (100 mg, 0.290 mmol) in THF (2.9 mL) was added triphenylphosphine (90 mg, 0.34 mmol). The reaction mixture was cooled to 0 ºC, and diethylazodicarboxylate (0.054 mL, 0.34 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for

16 h, and then concentrated under reduced pressure. Column chromatography (EtOAc + 1% NEt_3) using NEt_3-treated silica gel afforded 96.8 mg (99%) of **5.6** as a white foam. IR 3174, 2923, 1735, 1542, 1254, 1048, 959, 744 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 1.20 (s, 9H), 1.75 (s, 3H), 1.83 (s, 3H), 1.93-1.99 (m, 2H), 2.02-2.06 (m, 1H), 2.50-2.56 (m, 1H), 3.33 (s, 1H), 4.97 (d, 1H, *J* = 9.0), 5.35 (d, 1H, *J* = 9.0), 7.36-7.40 (m, 2H), 7.66-7.68 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.3, 14.3, 19.1, 22.8, 26.1, 37.8, 50.0, 55.5, 121.2, 124.2, 125.2, 127.6, 135.4, 136.6, 137.0, 157.3, 175.6. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{19}H_{27}N_2OS$, 331.1839; found, 331.1845.

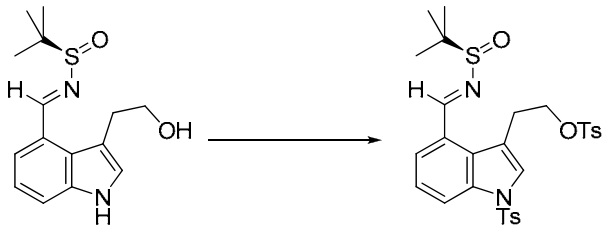


(R_S, *R*)-*N*-*tert*-Butanesulfinamide 5.11. This procedure was adapted from that reported by Qin for the tosylation of an indole derivative.[18] To a 0.2 M solution of sulfinamide **5.2** (20.0 mg, 0.060 mmol) in CH_2Cl_2 (0.3 mL) was added Et_3N (0.017 mL, 0.12 mmol) and 4-(dimethylamino)pyridine (1.5 mg, 0.012 mmol). The resulting solution was cooled to 0 ºC, and chlorotriethylsilane (0.01 mL, 0.06 mmol) was added dropwise. After stirring for 4 h at room temperature, the resulting mixture was diluted with CH_2Cl_2 (5 mL), washed with water (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. To a 0.2 M solution of the resulting residue in CH_2Cl_2 (0.3 mL) were added sequentially sodium hydroxide (7.2 mg, 0.18 mmol), Bu_4NHSO_4 (1.0 mg, 0.0030 mmol), and *p*-toluenesulfonyl chloride (13.7 mg, 0.072 mmol). After stirring the reaction mixture for 1 h, the suspension was diluted with CH_2Cl_2 (5 mL), filtered, and the filtrate was concentrated. To a 0.2 M solution of the resulting residue in THF (0.3 mL) at 0 ºC was added Bu_4NF (24.6 mg, 0.080 mmol). The resulting solution was stirred for 1 h at room temperature, then diluted with water (5 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with a saturated NaCl solution (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 70-100% EtOAc/hexanes) afforded 16.8 mg (56%) of **5.11**. ^1H NMR (500 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.756 (s, 3H), 1.762 (s, 3H), 2.35 (s, 3H), 3.08-3.14 (m, 1H), 3.22-3.28 (m, 1H), 3.61-3.72 (m, 2H), 3.93-3.98 (m, 1H), 5.48 (d, 1H, *J* = 9.0), 5.86 (d, 1H, *J* = 9.0), 7.24 (d, 2H, *J* = 8.0), 7.29 (t, 1H, *J* = 8.0), 7.37 (d, 1H, *J* = 7.0), 7.44 (s, 1H), 7.77 (d, 2H, *J* = 8.0), 7.93 (d, 1H, *J* = 7.5). MS (ESI): *m/z* 525 $[MNa]^+$.



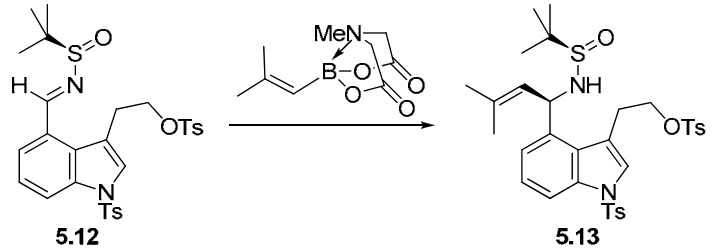
***(R_S, R)*-Azepine 5.7.** In an inert atmosphere box, tributylphosphine (9.1 mg, 0.045 mmol) was added to a 0.05 M solution of sulfinamide **5.11** (7.4 mg, 0.015 mmol) in THF (0.3

mL). The reaction flask was placed in a - 20 ºC freezer for 5 min, and then azodicarboxylic acid dipiperidine (11.4 mg, 0.045 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for 21 h, and then concentrated under reduced pressure. Column chromatography (SiO_2, 50% EtOAc/hexanes) afforded 5.1 mg (78%) of **5.7** as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.66 (s, 3H), 1.86 (s, 3H), 2.36 (s, 3H), 3.00-3.06 (m, 2H), 3.54-3.60 (m, 1H), 3.92-3.99 (m, 1H), 5.34 (d, 1H, *J* = 9.0), 5.67 (d, 1H, *J* = 9.0), 6.88 (d, 1H, *J* = 7.6), 7.19 (t, 1H, *J* = 8.0), 7.22 (d, 2H, *J* = 8.0), 7.38 (s, 1H), 7.74 (d, 2H, *J* = 8.0), 7.83 (d, 1H, *J* = 8.0). MS (ESI): *m/z* 485 $[MH]^+$. ^{1}H NMR shifts correspond exactly to when compound **5.7** was prepared from sulfinamide **5.13** (vide infra).



5.3 **5.12**

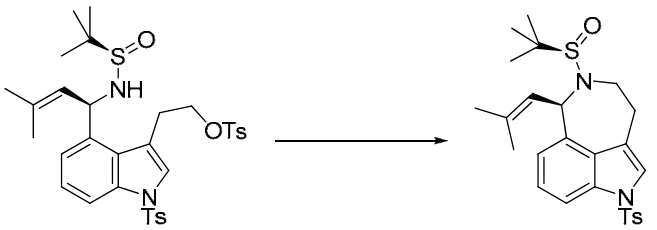
(*R*)-*N*-*tert*-butanesulfinyl aldimine 5.12. This procedure was adapted from that reported by Higuchi for the tosylation of a tryptophol derivative.[21] A 0.07 M solution of aldimine **5.3** (436 mg, 1.49 mmol) and NEt_3 (2.10 mL, 14.9 mmol) in CH_2Cl_2 (21 mL) was cooled to -20 ºC. 4-(Dimethylamino)pyridine (182 mg, 1.49 mmol) and *p*-toluenesulfonyl chloride (2.84 g, 14.9 mmol) were added. The reaction mixture was stirred at -20 ºC for 43 h. The resulting solution was washed with water (15 mL). The aqueous layer was then back extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 700 mg (78%) of **5.12** as an off-white foam. $[\alpha]_D^{23}$ −107.2º (*c* 1.0, $CHCl_3$). IR 2924, 1590, 1358, 1174, 1082 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (s, 9H), 2.33 (s, 3H), 2.36 (s, 3H), 3.18-3.23 (m, 1H), 3.27-3.32 (m, 1H), 4.24-4.28 (m, 1H), 4.30-4.34 (m, 1H), 7.12 (d, 2H, *J* = 8.0), 7.26 (d, 2H, *J* = 8.0), 7.36 (t, 1H, *J* = 8.5), 7.53 (d, 2H, *J* = 8.0), 7.55 (s, 1H), 7.78 (d, 2H, *J* = 8.0), 7.86 (d, 1H, *J* = 8.5), 8.14 (d, 1H, *J* = 8.5), 8.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.76, 21.79, 22.7, 28.0, 58.1, 68.5, 117.3, 117.5, 124.3, 124.6, 127.1, 127.5, 127.79, 127.82, 129.2, 129.9, 130.0, 132.4, 134.9, 136.4, 144.9, 145.6, 160.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{29}H_{33}N_2O_6S_3$, 601.1495; found, 601.1524.



5.12 **5.13**

(R_S, *R*)-*N*-*tert*-Butanesulfinamide 5.13. In an inert atmosphere box, hydroxy(1,5-cyclooctadiene)rhodium(I) dimer (1.4 mg, 0.0031 mmol) was dissolved in dioxane (0.2 mL), and the resulting solution was added to a pressure tube containing 1,2-

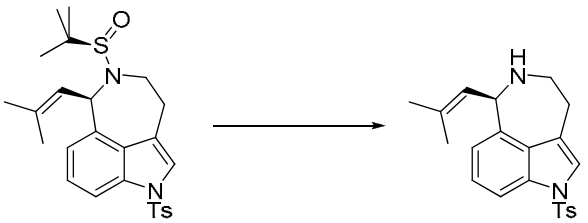
bis(diphenylphosphino)benzene (2.8 mg, 0.0063 mmol). The resulting mixture of catalyst and ligand was added to a 20-mL pressure tube containing a stirbar and MIDA boronate **5.9** (53 mg, 0.25 mmol). To the mixture of catalyst, ligand, and MIDA boronate was added sulfinyl imine **5.12** (75.1 mg, 0.125 mmol) dissolved in dioxane (0.2 mL), followed by water (0.6 mL), and K_3PO_4 (53.1 mg, 0.250 mmol). The pressure tube was capped, removed from the inert atmosphere box, heated to 60 °C, and stirred for 20 h. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL) and the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product (97:3 dr). Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 64.1 mg (78%, >99:1 dr) of **5.13** as a pale yellow foam. An authentic mixture of *N*-sulfinyl amine diastereomers for diastereoselectivity determination was prepared according to the general literature procedure by in situ sulfinyl cleavage with HCl followed by resulfinylation upon addition of NEt_3.[22] HPLC (silica column, hexanes:EtOH 90:10, 1.0 mL/min, λ = 220 nm): t_{major} = 12.7 min, t_{minor} = 16.5 min.). IR 3264, 2927, 1364, 1174, 1040 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H), 1.73 (s, 3H), 1.75 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 3.29 (app t, 2H, *J* = 6.0), 3.45 (s, 1H), 4.27-4.33 (m, 1H), 4.35-4.40 (m, 1H), 5.36 (d, 1H, *J* = 8.8), 5.56 (d, 1H, *J* = 8.8), 7.23 (d, 2H, *J* = 8.4), 7.24 (d, 2H, *J* = 8.4), 7.28 (t, 1H, *J* = 8.0), 7.36 (d, 1H, *J* = 7.6), 7.39 (s, 1H), 7.65 (d, 2H, *J* = 7.6), 7.75 (d, 2H, *J* = 8.4), 7.91 (d, 1H, *J* = 8.4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.7, 21.8, 22.8, 26.1, 27.3, 51.7, 55.5, 69.1, 113.2, 117.0, 122.7, 125.0, 125.2, 125.5, 127.1, 127.3, 127.9, 130.0, 130.2, 132.6, 135.1, 135.9, 136.1, 137.2, 145.0, 145.2. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{33}H_{41}N_2O_6S_3$, 657.2121; found, 657.2153.



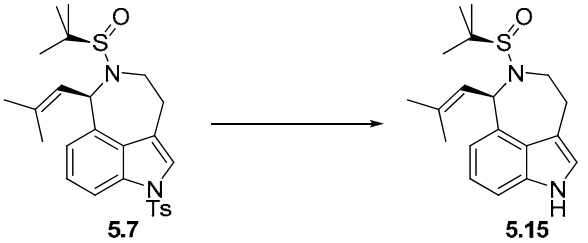
5.13 **5.7**

***(R_S, R)*-Azepine 5.7.** A 0.01 M solution of sulfinamide **5.13** (90.6 mg, 0.138 mmol) in THF (14.4 mL) was cooled to 0 ºC. NaH (11.5 mg, 0.29 mmol) was added, and the reaction mixture was stirred at 0 ºC for 10 min. The reaction mixture was then warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated aqueous NH_4Cl (15 mL), and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 57.0 mg (85%, >99:1 dr) of **5.7** as a white foam. HPLC (silica column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{major} = 33.3 min, t_{minor} = 35.7 min.). IR 2920, 1362, 1175, 1143, 1067, 934 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.64 (s, 3H), 1.86 (s, 3H), 2.33 (s, 3H), 2.97-3.08 (m, 2H), 3.54-3.56 (m, 1H), 3.92-3.98 (m, 1H), 5.34 (d, 1H, *J* = 9.0), 5.67 (d, 1H, *J* = 9.0), 6.88 (d, 1H, *J* = 7.5), 7.18 (t, 1H, *J* = 8.0), 7.21 (d, 2H, *J* = 8.3), 7.38 (s, 1H), 7.74 (d, 2H, *J* = 8.3), 7.83 (d, 1H, *J* = 8.3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.6, 21.7, 23.6, 26.5, 29.9, 46.6 (br), 57.2 (br),

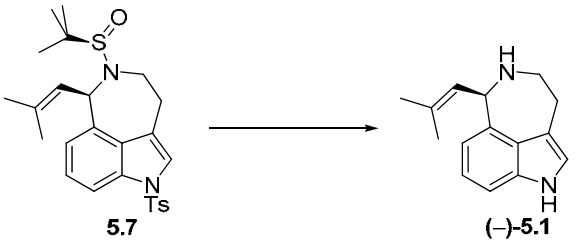
58.0, 111.9, 120.6, 121.8, 123.4, 123.6, 124.6, 127.0, 128.4, 130.0, 135.3, 135.4, 136.3, 138.9, 145.0. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{26}H_{33}N_2O_3S_2$, 485.1927; found, 485.1949.



***(R_S, R)*-Azepine 5.14.** To a 0.15 M solution of azepine **5.7** (30.0 mg, 0.061 mmol) in MeOH (0.4 mL) was added HCl (0.023 mL, 4 M in dioxane , 0.093 mmol). The reaction mixture was stirred at room temperature for 35 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and the resulting mixture was diluted with CH_2Cl_2 (5 mL). The organic layer was removed, and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product. Column chromatography (SiO_2, 50-80% EtOAc/hexanes + 1% NEt_3) using NEt_3-treated silica gel afforded 22.7 mg (98% yield) of **5.14** as a pale yellow oil. IR 3349, 2920, 1597, 1364, 1293, 1175, 1142, 1091, 907 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 1.79 (s, 3H), 1.82 (s, 3H), 1.94 (br s, 1H), 2.32 (s, 3H), 2.89-2.99 (m, 2H), 3.00-3.09 (m, 1H), 3.41-3.50 (m, 1H), 4.80 (d, 1H, *J* = 9.0), 5.36 (d, 1H, *J* = 9.0), 6.95 (d, 1H, *J* = 7.5), 7.16-7.21 (m, 3H), 7.36 (s, 1H), 7.73 (d, 2H, *J* = 8.0), 7.88 (d, 1H, *J* = 8.2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.5, 21.7, 26.0, 30.8, 48.0, 62.3, 111.9, 122.1, 122.5, 122.7, 124.2, 127.0, 127.3, 129.1, 129.9, 134.3, 135.5, 136.3, 139.4, 144.8. HRMS-FAB (m/z): $[MH]^+$ calcd for $C_{22}H_{25}N_2O_2S$, 381.1637; found, 381.1632.

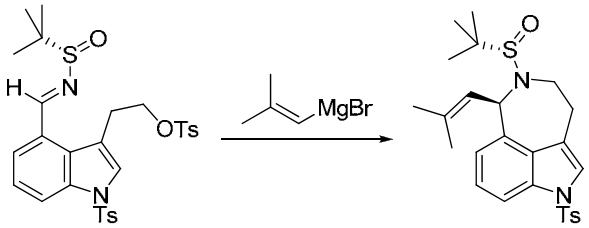


***(R_S, R)*-Azepine 5.15.** To a 0.05 M solution of azepine **5.7** (39.7 mg, 0.082 mmol) in anhydrous MeOH (1.6 mL) was added flame-dried Mg^0 powder (29.9 mg, 1.23 mmol). The mixture was stirred for 2 h and then concentrated under reduced pressure. After diluting with CH_2Cl_2, the reaction mixture was filtered through a pad of Celite and then concentrated under reduced pressure. Column chromatography (SiO_2, 50% EtOAc/hexanes) afforded 26.3 mg (97%) of **5.15** as a white solid. decomp >210 ºC. ^1H NMR (600 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.66 (s, 3H), 1.94 (s, 3H), 3.03-3.14 (m, 2H), 3.60-3.64 (m, 1H), 4.07-4.13 (m, 1H), 5.48 (d, 1H, *J* = 9.0), 5.80 (d, 1H, *J* = 9.0), 6.78 (d, 1H, *J* = 7.8), 7.00 (s, 1H), 7.08 (t, 1H, *J* = 7.8), 7.21 (d, 1H, *J* = 7.8), 8.44 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.7, 23.8, 26.6, 30.3, 47.9, 57.2, 57.9, 109.6, 114.2, 117.8, 121.88, 121.94, 124.4, 125.1, 134.3, 137.5, 137.9. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{19}H_{27}N_2OS$, 331.1839; found, 331.1854.



5.7 **(–)-5.1**

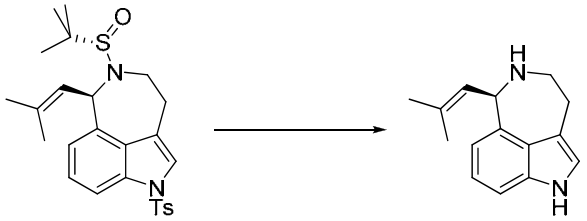
(–)-Aurantioclavine ((–)5.1). To a 0.05 M solution of sulfinamide **5.7** (56.0 mg, 0.115 mmol) in anhydrous MeOH (2.3 mL) was added HCl (0.043 mL, 4 M in dioxane, 0.173 mmol). After stirring the mixture for 30 min, flame-dried Mg^0 powder (28.1 mg, 1.15 mmol) was added. The reaction was followed by TLC and more Mg^0 powder (2 x 14.1 mg, 0.58 mmol) was added at hourly intervals until the reaction had gone to completion. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was removed and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 50-60% EtOAc/hexanes + 1% NEt_3) using NEt_3-treated silica gel afforded 25.9 mg (99% yield, >99% ee) of (–)-Aurantioclavine as an off-white solid. For enantiopurity determination, authentic (+)-Aurantioclavine was prepared by deprotection of **ent-5.16** following the same procedure as described above. HPLC (Chiralcel IA, hexanes:EtOH 96:4 + 1% Et_2NH, 1.0 mL/min, λ = 280 nm): t_R= 22.9 min, t_S = 27.5 min). mp 189.2-190.1 ºC (lit.[1] mp 188-189 ºC). $[\alpha]_D^{23}$ −28.3º (*c* 1.0, $CHCl_3$) [lit.[1] $[\alpha]_D^{22}$ −34 (*c* 1.25, $CHCl_3$)]. IR 3290, 3031, 2919, 1613, 1416, 1338, 1259, 1123, 881, 736 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 1.851 (s, 3H), 1.852 (s, 3H), 2.99-3.06 (m, 2H), 3.11-3.15 (m, 1H), 3.53-3.58 (m, 1H), 4.89 (d, 1H, *J* = 9.0), 5.46 (d, 1H, *J* = 9.0), 6.84 (d, 1H, *J* = 7.8), 7.02 (s, 1H), 7.10 (t, 1H, *J* = 7.8), 7.22 (d, 1H, *J* = 8.4), 8.08 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 26.0, 31.1, 49.1, 62.8, 109.4, 115.7, 118.0, 121.2, 121.6, 125.5, 127.9, 133.4, 137.3, 138.6. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{15}H_{19}N_2$, 227.1543; found, 227.1538. Characterization data matches both isolated natural[1] and synthetic[4] material [For a 100 MHz ^1H-NMR spectrum of isolated natural material, see page 231 in reference 8 and for 300 MHz ^1H-NMR and 75 MHz ^{13}C-NMR spectra of isolated synthetic material, see S19-S20 in the supporting information of reference 9].



ent-5.12 **5.16**

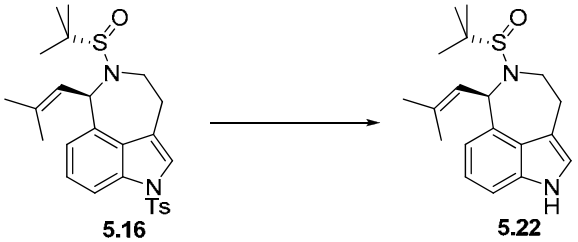
***(S*S*, R)*-Azepine 5.16.** To a 0.17 M solution of sulfinyl imine **ent-5.12** (785 mg, 1.31 mmol) in CH_2Cl_2 (7.9 mL) at -48 ºC was added dropwise a solution of 2-methyl-1-propenylmagnesium bromide (5.2 mL, 0.5 M in THF, 2.62 mmol). The reaction mixture was stirred at -48 ºC for 15 min and then warmed to room temperature with stirring overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the resulting mixture was diluted with EtOAc (20 mL). The organic layer was removed and the aqueous layer was back-

extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product (81:19 dr). Column chromatography (Biotage Flash+ cartridge, 12-100% methyl *t*-butyl ether/hexanes) afforded 456 mg (72%, >99:1 dr) of **5.16** as a white solid. HPLC (silica column, hexanes:EtOH 98:2, 1.0 mL/min, λ = 222 nm): t_{minor} = 35.5 min, t_{major} = 38.6 min.). mp 88.1-90.9 ºC. IR 2920, 1362, 1172, 1143, 1073, 938 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.70 (s, 3H), 1.92 (s, 3H), 2.34 (s, 3H), 3.05-3.08 (m, 2H), 3.22-3.28 (m, 1H), 3.64-3.68 (m, 1H), 5.45 (d, 1H, *J* = 9.5), 5.50 (d, 1H, *J* = 9.5), 6.89 (d, 1H, *J* = 7.0), 7.20 (t, 1H, *J* = 7.5), 7.24 (d, 2H, *J* = 8.0), 7.37 (s, 1H), 7.76 (d, 2H, *J* = 8.5), 7.83 (d, 1H, *J* = 8.0). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.0, 21.7, 23.2, 26.3, 28.1, 37.1 (br), 57.9, 65.8 (br), 112.0, 121.0, 121.8, 122.8, 123.8, 124.5, 127.1, 128.4, 130.0, 135.46, 135.52, 136.1, 137.8, 145.0. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{26}H_{33}N_2O_3S_2$, 485.1927; found, 485.1938.



5.16 (–)-**5.1**

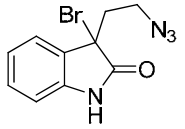
(–)-Aurantioclavine ((–)5.1). To a 0.05 M solution of sulfinamide **5.16** (10.6 mg, 0.022 mmol) in anhydrous MeOH (0.4 mL) was added HCl (0.008 mL, 4 M in dioxane, 0.173 mmol). After stirring the mixture for 30 min, flame-dried Mg^0 powder (8.0 mg, 0.33 mmol) was added. The reaction was followed by TLC and more Mg^0 powder (3 x 4.0 mg, 0.16 mmol) was added at hourly intervals until the reaction had gone to completion. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was removed and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (SiO_2, 50-60% EtOAc/hexanes + 1% NEt_3) using NEt_3-treated silica gel afforded 4.8 mg (98% yield, >99% ee) of (–)-Aurantioclavine as an off-white solid. HPLC (Chiralcel IA, hexanes:EtOH 96:4 + 1% Et_2NH, 1.0 mL/min, λ = 280 nm): t_R= 24.2 min). ^1H-NMR data corresponded to the data reported for the synthesis of (–)-Aurantioclavine by addition of the MIDA boronate (vide supra).



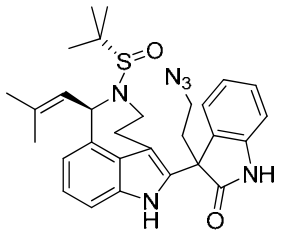
5.16 **5.22**

***(S*S*, *R*)*-Azepine 5.22.** To a 0.05 M solution of sulfinamide **5.16** (43.0 mg, 0.115 mmol) in anhydrous MeOH (1.8 mL) was added flame-dried Mg^0 powder (32.3 mg, 1.33 mmol). The mixture was stirred for 2 h and then concentrated under reduced pressure. After diluting with CH_2Cl_2, the reaction mixture was filtered through a pad of Celite and then concentrated under

reduced pressure. Column chromatography (SiO_2, 50% EtOAc/hexanes) afforded 27.2 mg (93%) of **5.22** as a white solid. decomp >195 ºC. IR 3218, 2921, 1733, 1426, 1362, 1118, 1037, 888, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H), 1.72 (s, 3H), 1.98 (s, 3H), 3.11-3.16 (m, 2H), 3.30-3.38 (m, 1H), 3.74-3.79 (m, 1H), 5.59 (d, 1H, *J* = 9.6), 5.63 (d, 1H, *J* = 9.6), 6.78 (d, 1H, *J* = 7.2), 7.02 (s, 1H), 7.09 (t, 1H, *J* = 7.6), 7.22 (d, 1H, *J* = 7.6), 8.18 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.0, 23.4, 26.4, 28.5, 37.4, 57.8, 66.9, 109.6, 114.7, 117.8, 121.4, 121.8, 124.8, 124.9, 134.4, 136.7, 137.3. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{19}H_{27}N_2OS$, 331.1839; found, 331.1853.

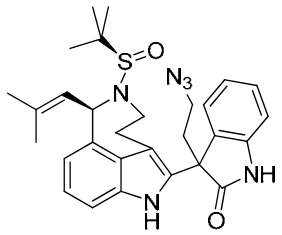


3-Bromo-indolinone 5.23. This procedure was adapted from that reported by Bauman for the synthesis of 3-bromo-3-methoxyindole.[23] *t*-BuOH (80 mL) was purified immediately prior to use by distilling over NaH (4 g), followed by treatment with activated carbon (0.8 g) and 3Å MS, and filtration under a nitrogen atmosphere. (3-(2-Azidoethyl)indole[24] (200 mg, 1.07 mmol) was dissolved in *t*-BuOH (7.3 mL) in a Schlenk flask and placed in an ambient water bath. *N*-Bromo-succinimide (383 mg, 2.15 mmol) was then added over a period of 1 h in small portions at 10 min intervals. After stirring the reaction mixture for an additional 2 h at room temperature, the mixture was concentrated under reduced pressure. Column chromatography (SiO_2, 5-40% EtOAc/hexanes) afforded 133 mg (44%) of **5.23** as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$): δ 2.56-2.65 (m, 1H), 2.73-2.82 (m, 1H), 3.20-3.28 (m, 1H), 3.32-3.40 (m, 1H), 6.93 (d, 1H, *J* = 7.8), 7.12 (dt, 1H, *J* = 7.6, 0.8), 7.31 (dt, 1H, *J* = 7.8, 1.2), 7.40 (d, 1H, *J* = 7.6), 8.00 (br s, 1H). MS (ESI): *m/z* 281 $[MH]^+$

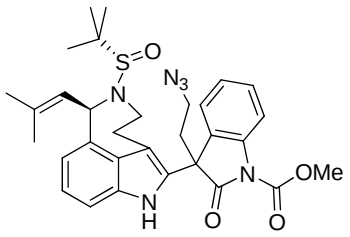


Indole 5.24. To a 0.3 M solution of azepine **5.22** (76 mg, 0.23 mmol) and cesium carbonate (170 mg, 0.54 mmol) in CH_2Cl_2 (0.75 mL) at room temperature, was added a 0.2 M solution of 3-bromo-indolinone **5.23** (43 mg, 0.15 mmol) in CH_2Cl_2 (0.75 mL) over a period of 1 h. The solution was stirred for 16 h at room temperature. The reaction mixture was then filtered through a pad of silica, washed thoroughly with CH_2Cl_2, and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 40-100% EtOAc/hexanes) afforded 53.3 mg (66%; 55:45 dr) of **5.24**. ^1H NMR (600 MHz, $CDCl_3$): δ 0.99 (s, 4H), 1.13 (s, 5H), 1.66 (s, 1.4H), 1.69 (s, 1.6H), 1.92 (s, 1.4H), 1.96 (s, 1.6H), 2.24-2.33 (m, 0.55H), 2.35-2.43 (m, 0.45H), 2.55-2.64 (m, 1H), 2.76-2.85 (m, 1H), 2.86-2.95 (m, 1H), 3.08-3.28 (m, 3H), 3.41-3.48 (m, 0.45H), 3.49-3.57 (m, 0.55H), 5.49 (d, 0.45H, *J* = 9.6), 5.55 (d, 0.55H, *J* = 9.6), 5.57 (s, 1H), 6.66 (d, 0.45H, *J* = 7.3), 6.74 (d, 0.55H, *J* = 7.2), 6.86-6.92 (m, 1H), 6.93 (d, 0.45H, *J* = 7.9), 6.98 (d, 0.55H, *J* = 7.7), 7.00-7.06 (m, 1.45H), 7.07-7.11 (m, 1H), 7.17 (d, 0.55H, *J* = 7.2),

7.19-7.25 (m, 1H), 8.82 (br s, 0.55H), 9.27 (br s, 0.45H), 9.51 (br s, 0.45H), 9.66 (br s, 0.55H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.91, 18.92, 23.3, 23.4, 26.2, 26.3, 27.7, 27.8, 35.1, 35.3, 37.0, 37.7, 47.1, 47.2, 52.4, 57.8, 57.9, 66.4, 109.5, 109.6, 110.9, 111.1, 111.9, 112.4, 118.4, 121.7, 121.8, 123.1, 123.2, 124.6, 124.7, 124.9, 126.0, 126.3, 129.3, 129.4, 129.8, 130.2, 130.4, 134.4, 134.6, 135.9, 136.15, 136.19, 136.23, 141.6, 178.6, 178.8. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{29}H_{35}N_6O_2S$, 531.2537; found, 531.2535.

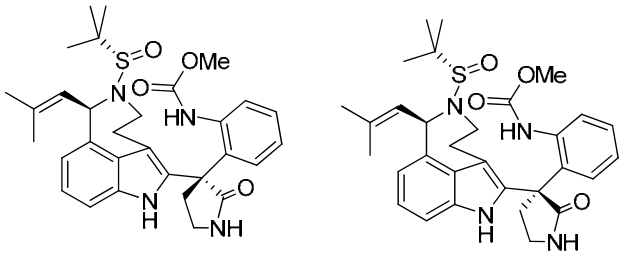


Indole 5.25. To a 0.3 M solution of azepine **5.15** (9 mg, 0.03 mmol) and cesium carbonate (34 mg, 0.11 mmol) in CH_2Cl_2 (0.15 mL) at room temperature, was added a 0.2 M solution of 3-bromo-indolinone **5.23** (15 mg, 0.05 mmol) in CH_2Cl_2 (0.15 mL) over a period of 1 h. The solution was stirred for 21 h at room temperature. The reaction mixture was then filtered through a pad of silica, washed thoroughly with CH_2Cl_2, and concentrated under reduced pressure afford the crude product (85:15 dr). Column chromatography (Biotage Flash+ cartridge, 12-100% EtOAc/hexanes) afforded 10.2 mg (8.7 mg major and 1.5 mg minor; 64%) of **5.24**. Major: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.67 (s, 3H), 1.94 (s, 3H), 2.57-2.61 (m, 1H), 2.72-2.77 (m, 2H), 2.79-2.83 (m, 1H), 3.15-3.19 (m, 1H), 3.24-3.28 (m, 1H), 3.38-3.43 (m, 1H), 3.82-3.90 (m, 1H), 5.45 (d, 1H, *J* = 9.6), 5.71 (d, 1H, *J* = 9.6), 6.76 (d, 1H, *J* = 7.2), 6.97 (d, 1H, *J* = 7.8), 7.05 (t, 1H, *J* = 7.8), 7.12 (t, 1H, *J* = 7.8), 7.16 (d, 1H, *J* = 7.8), 7.20 (d, 1H, *J* = 7.2), 7.32 (t, 1H, *J* = 7.8), 8.33 (br s, 1H), 8.34 (br s, 1H). MS (ESI): *m/z* 531 $[MNa]^+$. Minor: ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.66 (s, 3H), 1.90 (s, 3H), 2.24-2.33 (m, 1H), 2.50-2.59 (m, 2H), 2.78-2.84 (m, 1H), 3.16-3.23 (m, 1H), 3.25-3.31 (m, 1H), 3.32-3.39 (m, 1H), 3.86-3.92 (m, 1H), 5.44 (d, 1H, *J* = 9.6), 5.68 (d, 1H, *J* = 9.0), 6.75 (d, 1H, *J* = 7.2), 6.98 (d, 1H, *J* = 7.2), 7.02-7.12 (m, 3H), 7.19 (d, 1H, *J* = 7.8), 7.33 (t, 1H, *J* = 7.2), 7.66 (br s, 1H), 8.44 (br s, 1H). MS (ESI): *m/z* 531 $[MNa]^+$.



Indole 5.27. Indole **5.24** (53 mg, 0.10 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C in an ice bath. Sodium hydride (4.1 mg of 60% NaH in mineral oil, 0.20 mmol) was added and the solution was stirred for ten min before the addition of methyl chloroformate (12 μL, 0.15 mmol). The resulting solution was warmed to room temperature and stirred for 1.5 h. The reaction was quenched with water, and the resulting solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 12-100%

EtOAc/hexanes) afforded 47.2 mg (80%; 55:45 dr) of **5.27** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ δ 1.00 (s, 4H), 1.12 (s, 5H), 1.67 (s, 1.6H), 1.68 (s, 1.4H), 1.91 (s, 1.4H), 1.92 (s, 1.6H), 2.33-2.47 (m, 1H), 2.54-2.58 (m, 1H), 2.79-2.88 (m, 1H), 2.93-2.98 (m, 1H), 3.07-3.13 (m, 1H), 3.15-3.24 (m, 2H), 3.40-3.48 (m, 0.45H), 3.52-3.58 (m, 0.55H), 4.01 (s, 1.6H), 4.02 (1.4H), 5.46-5.58 (m, 2H), 6.74 (app t, 1H, *J* = 9.6), 7.03 (t, 1H, *J* = 9.3), 7.10-7.18 (m, 1.55H), 7.23-7.29 (m, 1.45H), 7.41-7.49 (m, 1H), 8.04-8.06 (m, 1H), 8.50 (br s, 0.55H), 8.72 (br s, 0.45H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.9, 19.0, 23.28, 23.33, 26.3, 27.88, 27.91, 35.6, 35.9, 37.2, 37.5, 47.1, 47.3, 52.3, 52.5, 54.35, 54.37, 57.7, 57.8, 65.9, 109.50, 109.54, 112.9, 113.4, 116.0, 116.1, 118.6, 118.7, 122.15, 122.18, 124.5, 124.6, 124.7, 125.5, 125.7, 126.2, 126.4, 128.0, 128.3, 129.1, 129.2, 129.9, 130.0, 134.3, 134.8, 135.8, 136.1, 136.6, 136.8, 139.7, 139.8, 151.38, 151.43, 174.6, 174.7. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{31}H_{37}N_6O_4S$, 589.2592; found, 589.2602.



Indole 5.26. Triphenylphosphine (42 mg, 0.16 mmol) was added to a stirred solution of indole **5.27** (47 mg, 0.080 mmol) in THF (0.8 mL) and water (0.2 mL) at room temperature. The resulting solution was then heated at 50 °C for five hours. The solution was cooled to room temperature and treated with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude product (55:45 dr). To remove the triphenylphosphine byproduct, the crude reaction mixture was purified by reverse phase chromatography (Biotage C18SH column, CH_3CN/H_2O = 5:95 to 95:5). The fractions containing product were combined, and the acetonitrile was removed by concentrating under reduced pressure. The remaining aqueous solvent was basified with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (Biotage Flash+ cartridge, 40-100% EtOAc/hexanes + 1% MeOH) was then used to separate the diastereomers to afford 42 mg (16 mg major, 12 mg minor, and 14 mg mixed, 93%) of **5.26** as a white solid. Crystallization of the major diastereomer by vapor diffusion of pentane into a solution of **5.26**-major in toluene and a drop of MeOH at 4 ºC yielded x-ray quality crystals. Major: IR 3412, 2921, 2852, 1741, 1683, 1453, 1228, 1034 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.70 (s, 3H), 1.92 (s, 3H), 2.12-2.21 (m, 1H), 2.45-2.52 (m, 1H), 2.90 (s, 3H), 3.11-3.20 (m, 1H), 3.35-3.39 (m, 1H), 3.41-3.49 (m, 1H), 3.56-3.61 (m, 1H), 3.66-3.73 (m, 1H), 5.47 (d, 1H, *J* = 9.6), 5.55 (d, 1H, *J* = 9.6), 6.19 (br s, 1H), 6.70 (d, 1H, *J* = 7.2), 7.01 (t, 1H, *J* = 7.8), 7.18 (d, 1H, *J* = 7.8), 7.22 (t, 1H, *J* = 7.8), 7.34 (t, 1H, *J* = 7.8), 7.53 (d, 1H, *J* = 7.8), 7.62 (br s, 1H), 8.71 (br s, 1H), 8.84 (br s, 1H).. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{31}H_{39}N_4O_4S$, 563.2687; found, 563.2705. ^{13}C NMR (150 MHz, $CDCl_3$): δ 18.9, 23.1, 26.4, 27.8, 35.3, 36.9, 40.4, 51.3, 51.5, 57.7, 66.2, 109.5, 110.8, 118.0, 121.4, 124.9, 125.5, 126.2, 127.4, 128.8, 134.0, 134.1, 136.0, 136.1, 138.4, 154.8, 178.6. Minor: ^{1}H NMR (600 MHz,

$CDCl_3$): δ 1.12 (s, 9H), 1.69 (s, 3H), 1.94 (s, 3H), 2.35-2.42 (m, 1H), 2.66-2.71 (m, 1H), 2.76 (br s, 3H), 2.82-2.87 (m, 1H), 3.11-3.19 (m, 1H), 3.24-3.27 (m, 1H), 3.49-3.57 (m, 2H), 3.64-3.69 (m, 1H), 5.54 (d, 1H, *J* = 9.6), 5.62 (d, 1H, *J* = 9.6), 6.54 (br s, 1H), 6.70 (d, 1H, *J* = 7.8), 6.99 (t, 1H, *J* = 7.8), 7.10 (d, 1H, *J* = 7.8), 7.26 (t, 1H, *J* = 7.8), 7.38 (t, 1H, *J* = 7.8), 7.48 (s, 1H), 7.54 (d, 1H, *J* = 7.8), 8.53 (br s, 1H), 8.78 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.0, 23.3, 26.3, 28.0, 35.6, 36.9, 40.4, 45.2, 51.3, 51.4, 57.7, 109.3, 110.4, 118.0, 121.6, 125.1, 125.5, 125.7, 126.1, 129.0, 129.3, 134.1, 136.1, 136.8, 138.2, 155.3, 178.1. HRMS-ESI (m/z): $[MH]^+$ calcd for $C_{31}H_{39}N_4O_4S$, 563.2687; found, 563.2693.

References

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Appendix 5.1: X-ray Crystal Data for 5.26-major

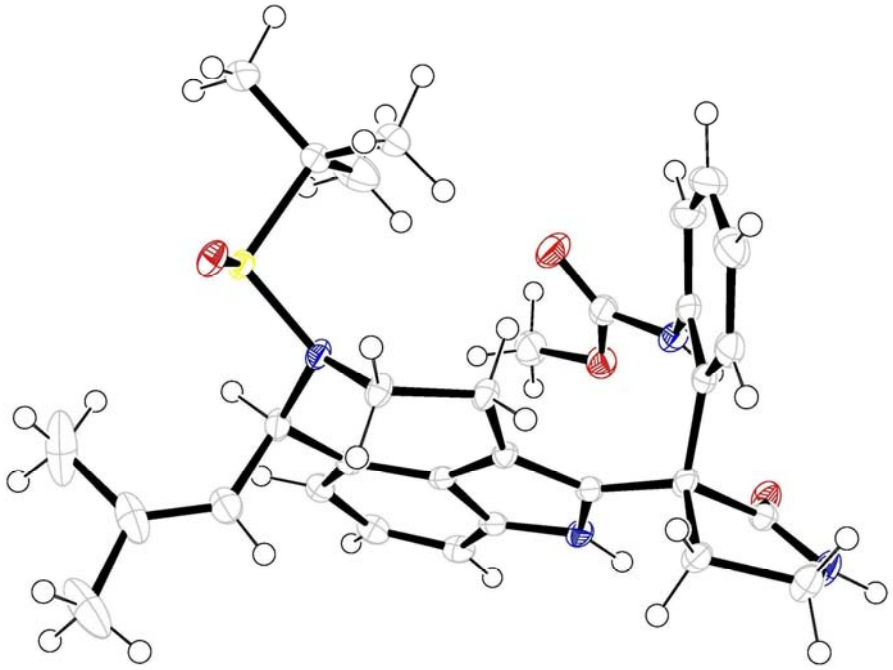

Figure A5.1.1 X-ray crystal structure of **5.26**-major with thermal ellipsoids drawn at the 50% probability level.

Data collection paramaters. A colorless block 0.10 x 0.10 x 0.05 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 0.5°. Data collection was 97.6% complete to 67.00° in θ. A total of 11917 reflections were collected covering the indices, -8<=*h*<=8, -9<=*k*<=11, -14<=*l*<=14. 4725 reflections were found to be symmetry independent, with an R_{int} of 0.0101. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P1 (No. 1). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2004) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Table A5.1.1. Crystal data and structure refinement for **5.26**-major

Empirical formula	$C_{31}H_{38}N_4O_4S$	
Formula weight	562.71	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 7.4890(5) Å	α = 68.741(2)°.
	b = 9.3695(6) Å	β = 78.076(2)°.
	c = 12.3607(8) Å	γ = 67.599(2)°.
Volume	744.95(8) $Å^3$	
Z	1	
Density (calculated)	1.254 Mg/m^3	
Absorption coefficient	1.301 mm^{-1}	
F(000)	300	
Crystal size	0.10 x 0.10 x 0.05 mm^3	
Crystal color/habit	colorless block	
Theta range for data collection	3.85 to 68.08°.	
Index ranges	-8<=h<=8, -9<=k<=11, -14<=l<=14	
Reflections collected	11917	
Independent reflections	4725 [R(int) = 0.0101]	

Completeness to theta = 67.00°	97.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9378 and 0.8809
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4725 / 3 / 367
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0265, wR2 = 0.0720
R indices (all data)	R1 = 0.0266, wR2 = 0.0721
Absolute structure parameter	0.009(9)
Largest diff. peak and hole	0.271 and -0.241 e.$Å^{-3}$

Table A5.1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5.26**-major. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

atom	x	y	z	U(eq)
C(1)	3879(2)	2642(2)	-207(1)	19(1)
C(2)	4165(2)	4183(2)	-1075(1)	18(1)
C(3)	4077(2)	5377(2)	-641(1)	20(1)
C(4)	4101(2)	6921(2)	-1360(2)	22(1)
C(5)	4196(2)	7322(2)	-2556(1)	21(1)
C(6)	4337(2)	6119(2)	-3008(1)	17(1)
C(7)	4369(2)	4531(2)	-2301(1)	16(1)
C(8)	4650(2)	3612(2)	-3076(1)	16(1)
C(9)	4758(2)	4651(2)	-4186(1)	16(1)
C(10)	4948(2)	1835(2)	-2761(1)	18(1)
C(11)	4118(2)	1083(2)	-1548(1)	18(1)
C(12)	1728(3)	2920(2)	95(2)	25(1)
C(13)	823(3)	2595(3)	1151(2)	36(1)
C(14)	-1352(4)	2986(3)	1303(2)	54(1)
C(15)	1816(5)	1807(5)	2272(2)	69(1)
C(16)	3414(2)	4883(2)	-7012(1)	24(1)
C(17)	3238(2)	4291(2)	-5676(1)	19(1)

C(18)	5111(2)	4302(2)	-5337(1)	18(1)
C(19)	5469(2)	5740(2)	-6389(1)	20(1)
C(20)	6866(2)	2740(2)	-5279(1)	19(1)
C(21)	6744(3)	1418(2)	-5497(1)	24(1)
C(22)	8244(3)	-73(2)	-5259(2)	32(1)
C(23)	9878(3)	-257(2)	-4802(2)	35(1)
C(24)	10077(2)	1050(2)	-4630(2)	30(1)
C(25)	8615(2)	2550(2)	-4890(1)	22(1)
C(26)	9357(2)	3923(2)	-3771(1)	25(1)
C(27)	9311(3)	5711(3)	-2827(2)	34(1)
C(28)	8367(2)	-1341(2)	-57(1)	21(1)
C(29)	9288(3)	-35(3)	-390(2)	38(1)
C(30)	8515(3)	-1987(2)	-1048(2)	28(1)
C(31)	9242(3)	-2754(3)	1011(2)	33(1)
N(1)	4939(2)	1211(2)	-613(1)	18(1)
N(2)	4499(2)	6173(2)	-4150(1)	18(1)
N(3)	4521(2)	5968(2)	-7268(1)	23(1)
N(4)	8831(2)	3911(2)	-4764(1)	22(1)
O(1)	4904(2)	-1693(1)	604(1)	21(1)
O(2)	6482(2)	6523(2)	-6399(1)	23(1)
O(3)	10038(2)	2760(2)	-2960(1)	34(1)
O(4)	9007(2)	5483(2)	-3856(1)	27(1)
S(1)	5832(1)	-473(1)	486(1)	16(1)

Table A5.1.3. Bond lengths [Å] for **5.26**-major

bond	distance	bond	distance
C(1)-N(1)	1.481(2)	C(17)-H(17B)	0.9900
C(1)-C(2)	1.517(2)	C(18)-C(20)	1.540(2)
C(1)-C(12)	1.519(2)	C(18)-C(19)	1.561(2)
C(1)-H(1)	1.0000	C(19)-O(2)	1.236(2)
C(2)-C(3)	1.381(2)	C(19)-N(3)	1.329(2)
C(2)-C(7)	1.419(2)	C(20)-C(21)	1.397(3)
C(3)-C(4)	1.401(2)	C(20)-C(25)	1.414(2)

C(3)-H(3)	0.9500	C(21)-C(22)	1.394(3)
C(4)-C(5)	1.380(2)	C(21)-H(21)	0.9500
C(4)-H(4)	0.9500	C(22)-C(23)	1.379(3)
C(5)-C(6)	1.390(2)	C(22)-H(22)	0.9500
C(5)-H(5)	0.9500	C(23)-C(24)	1.381(3)
C(6)-N(2)	1.376(2)	C(23)-H(23)	0.9500
C(6)-C(7)	1.420(2)	C(24)-C(25)	1.386(3)
C(7)-C(8)	1.442(2)	C(24)-H(24)	0.9500
C(8)-C(9)	1.372(2)	C(25)-N(4)	1.410(2)
C(8)-C(10)	1.503(2)	C(26)-O(3)	1.203(2)
C(9)-N(2)	1.380(2)	C(26)-O(4)	1.351(2)
C(9)-C(18)	1.523(2)	C(26)-N(4)	1.369(2)
C(10)-C(11)	1.521(2)	C(27)-O(4)	1.438(2)
C(10)-H(10A)	0.9900	C(27)-H(27A)	0.9800
C(10)-H(10B)	0.9900	C(27)-H(27B)	0.9800
C(11)-N(1)	1.4750(19)	C(27)-H(27C)	0.9800
C(11)-H(11A)	0.9900	C(28)-C(29)	1.517(2)
C(11)-H(11B)	0.9900	C(28)-C(30)	1.521(2)
C(12)-C(13)	1.326(3)	C(28)-C(31)	1.534(2)
C(12)-H(12)	0.9500	C(28)-S(1)	1.8463(16)
C(13)-C(15)	1.510(4)	C(29)-H(29A)	0.9800
C(13)-C(14)	1.514(3)	C(29)-H(29B)	0.9800
C(14)-H(14A)	0.9800	C(29)-H(29C)	0.9800
C(14)-H(14B)	0.9800	C(30)-H(30A)	0.9800
C(14)-H(14C)	0.9800	C(30)-H(30B)	0.9800
C(15)-H(15A)	0.9800	C(30)-H(30C)	0.9800
C(15)-H(15B)	0.9800	C(31)-H(31A)	0.9800
C(15)-H(15C)	0.9800	C(31)-H(31B)	0.9800
C(16)-N(3)	1.456(2)	C(31)-H(31C)	0.9800
C(16)-C(17)	1.534(2)	N(1)-S(1)	1.6728(13)
C(16)-H(16A)	0.9900	N(2)-H(2)	0.8800
C(16)-H(16B)	0.9900	N(3)-H(3A)	0.8800
C(17)-C(18)	1.550(2)	N(4)-H(4A)	0.8800
C(17)-H(17A)	0.9900	O(1)-S(1)	1.5017(12)

Table A5.1.4. Bond angles [°] for **5.26**-major

bond	angle	bond	angle
N(1)-C(1)-C(2)	111.97(12)	C(20)-C(18)-C(17)	114.57(14)
N(1)-C(1)-C(12)	113.96(13)	C(9)-C(18)-C(19)	112.07(14)
C(2)-C(1)-C(12)	109.44(13)	C(20)-C(18)-C(19)	109.72(12)
N(1)-C(1)-H(1)	107.0	C(17)-C(18)-C(19)	99.84(11)
C(2)-C(1)-H(1)	107.0	O(2)-C(19)-N(3)	125.96(14)
C(12)-C(1)-H(1)	107.0	O(2)-C(19)-C(18)	125.31(14)
C(3)-C(2)-C(7)	117.87(15)	N(3)-C(19)-C(18)	108.73(14)
C(3)-C(2)-C(1)	117.44(14)	C(21)-C(20)-C(25)	117.75(15)
C(7)-C(2)-C(1)	124.51(14)	C(21)-C(20)-C(18)	122.04(14)
C(2)-C(3)-C(4)	122.72(15)	C(25)-C(20)-C(18)	119.93(15)
C(2)-C(3)-H(3)	118.6	C(22)-C(21)-C(20)	121.04(17)
C(4)-C(3)-H(3)	118.6	C(22)-C(21)-H(21)	119.5
C(5)-C(4)-C(3)	120.65(16)	C(20)-C(21)-H(21)	119.5
C(5)-C(4)-H(4)	119.7	C(23)-C(22)-C(21)	119.86(19)
C(3)-C(4)-H(4)	119.7	C(23)-C(22)-H(22)	120.1
C(4)-C(5)-C(6)	117.33(15)	C(21)-C(22)-H(22)	120.1
C(4)-C(5)-H(5)	121.3	C(22)-C(23)-C(24)	120.33(17)
C(6)-C(5)-H(5)	121.3	C(22)-C(23)-H(23)	119.8
N(2)-C(6)-C(5)	129.48(14)	C(24)-C(23)-H(23)	119.8
N(2)-C(6)-C(7)	107.27(14)	C(23)-C(24)-C(25)	120.29(17)
C(5)-C(6)-C(7)	123.25(14)	C(23)-C(24)-H(24)	119.9
C(2)-C(7)-C(6)	118.03(14)	C(25)-C(24)-H(24)	119.9
C(2)-C(7)-C(8)	134.90(15)	C(24)-C(25)-N(4)	120.92(15)
C(6)-C(7)-C(8)	107.06(13)	C(24)-C(25)-C(20)	120.45(17)
C(9)-C(8)-C(7)	106.41(14)	N(4)-C(25)-C(20)	118.63(15)
C(9)-C(8)-C(10)	125.47(14)	O(3)-C(26)-O(4)	124.93(17)
C(7)-C(8)-C(10)	127.93(13)	O(3)-C(26)-N(4)	126.86(19)
C(8)-C(9)-N(2)	109.95(14)	O(4)-C(26)-N(4)	108.20(14)
C(8)-C(9)-C(18)	128.69(15)	O(4)-C(27)-H(27A)	109.5
N(2)-C(9)-C(18)	121.36(13)	O(4)-C(27)-H(27B)	109.5
C(8)-C(10)-C(11)	115.01(13)	H(27A)-C(27)-H(27B)	109.5
C(8)-C(10)-H(10A)	108.5	O(4)-C(27)-H(27C)	109.5

C(11)-C(10)-H(10A)	108.5	H(27A)-C(27)-H(27C)	109.5
C(8)-C(10)-H(10B)	108.5	H(27B)-C(27)-H(27C)	109.5
C(11)-C(10)-H(10B)	108.5	C(29)-C(28)-C(30)	113.08(15)
H(10A)-C(10)-H(10B)	107.5	C(29)-C(28)-C(31)	111.18(15)
N(1)-C(11)-C(10)	113.26(13)	C(30)-C(28)-C(31)	109.70(15)
N(1)-C(11)-H(11A)	108.9	C(29)-C(28)-S(1)	107.20(12)
C(10)-C(11)-H(11A)	108.9	C(30)-C(28)-S(1)	112.27(11)
N(1)-C(11)-H(11B)	108.9	C(31)-C(28)-S(1)	102.94(11)
C(10)-C(11)-H(11B)	108.9	C(28)-C(29)-H(29A)	109.5
H(11A)-C(11)-H(11B)	107.7	C(28)-C(29)-H(29B)	109.5
C(13)-C(12)-C(1)	127.06(18)	H(29A)-C(29)-H(29B)	109.5
C(13)-C(12)-H(12)	116.5	C(28)-C(29)-H(29C)	109.5
C(1)-C(12)-H(12)	116.5	H(29A)-C(29)-H(29C)	109.5
C(12)-C(13)-C(15)	124.6(2)	H(29B)-C(29)-H(29C)	109.5
C(12)-C(13)-C(14)	120.4(2)	C(28)-C(30)-H(30A)	109.5
C(15)-C(13)-C(14)	114.9(2)	C(28)-C(30)-H(30B)	109.5
C(13)-C(14)-H(14A)	109.5	H(30A)-C(30)-H(30B)	109.5
C(13)-C(14)-H(14B)	109.5	C(28)-C(30)-H(30C)	109.5
H(14A)-C(14)-H(14B)	109.5	H(30A)-C(30)-H(30C)	109.5
C(13)-C(14)-H(14C)	109.5	H(30B)-C(30)-H(30C)	109.5
H(14A)-C(14)-H(14C)	109.5	C(28)-C(31)-H(31A)	109.5
H(14B)-C(14)-H(14C)	109.5	C(28)-C(31)-H(31B)	109.5
C(13)-C(15)-H(15A)	109.5	H(31A)-C(31)-H(31B)	109.5
C(13)-C(15)-H(15B)	109.5	C(28)-C(31)-H(31C)	109.5
H(15A)-C(15)-H(15B)	109.5	H(31A)-C(31)-H(31C)	109.5
C(13)-C(15)-H(15C)	109.5	H(31B)-C(31)-H(31C)	109.5
H(15A)-C(15)-H(15C)	109.5	C(11)-N(1)-C(1)	116.93(12)
H(15B)-C(15)-H(15C)	109.5	C(11)-N(1)-S(1)	118.66(11)
N(3)-C(16)-C(17)	101.81(13)	C(1)-N(1)-S(1)	111.91(10)
N(3)-C(16)-H(16A)	111.4	C(6)-N(2)-C(9)	109.17(12)
C(17)-C(16)-H(16A)	111.4	C(6)-N(2)-H(2)	125.4
N(3)-C(16)-H(16B)	111.4	C(9)-N(2)-H(2)	125.4
C(17)-C(16)-H(16B)	111.4	C(19)-N(3)-C(16)	114.44(13)
H(16A)-C(16)-H(16B)	109.3	C(19)-N(3)-H(3A)	122.8
C(16)-C(17)-C(18)	104.46(12)	C(16)-N(3)-H(3A)	122.8

C(16)-C(17)-H(17A)	110.9	C(26)-N(4)-C(25)	124.10(14)
C(18)-C(17)-H(17A)	110.9	C(26)-N(4)-H(4A)	117.9
C(16)-C(17)-H(17B)	110.9	C(25)-N(4)-H(4A)	117.9
C(18)-C(17)-H(17B)	110.9	C(26)-O(4)-C(27)	114.88(14)
H(17A)-C(17)-H(17B)	108.9	O(1)-S(1)-N(1)	109.56(6)
C(9)-C(18)-C(20)	109.37(12)	O(1)-S(1)-C(28)	104.86(7)
C(9)-C(18)-C(17)	111.02(12)	N(1)-S(1)-C(28)	103.42(7)

Table A5.1.5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5.26**-major. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	26(1)	16(1)	14(1)	-5(1)	1(1)	-7(1)
C(2)	15(1)	16(1)	19(1)	-4(1)	-2(1)	-3(1)
C(3)	20(1)	20(1)	22(1)	-8(1)	-1(1)	-5(1)
C(4)	20(1)	20(1)	30(1)	-12(1)	0(1)	-7(1)
C(5)	19(1)	12(1)	29(1)	-4(1)	-1(1)	-7(1)
C(6)	14(1)	14(1)	20(1)	-3(1)	-2(1)	-3(1)
C(7)	13(1)	13(1)	19(1)	-2(1)	-2(1)	-4(1)
C(8)	14(1)	16(1)	15(1)	-2(1)	-2(1)	-6(1)
C(9)	14(1)	15(1)	17(1)	-3(1)	-1(1)	-5(1)
C(10)	24(1)	15(1)	14(1)	-2(1)	-2(1)	-7(1)
C(11)	26(1)	15(1)	15(1)	-2(1)	-3(1)	-10(1)
C(12)	29(1)	17(1)	26(1)	-6(1)	5(1)	-9(1)
C(13)	46(1)	32(1)	36(1)	-19(1)	20(1)	-24(1)
C(14)	49(1)	50(2)	71(2)	-36(1)	37(1)	-31(1)
C(15)	94(2)	106(3)	27(1)	-22(1)	21(1)	-67(2)
C(16)	27(1)	28(1)	19(1)	-1(1)	-5(1)	-14(1)
C(17)	18(1)	21(1)	17(1)	-2(1)	-4(1)	-8(1)
C(18)	18(1)	18(1)	14(1)	0(1)	-1(1)	-8(1)
C(19)	18(1)	18(1)	17(1)	-1(1)	0(1)	-5(1)
C(20)	22(1)	19(1)	13(1)	-1(1)	2(1)	-7(1)
C(21)	29(1)	23(1)	17(1)	-3(1)	2(1)	-9(1)
C(22)	40(1)	22(1)	27(1)	-8(1)	8(1)	-9(1)

C(23)	28(1)	25(1)	31(1)	0(1)	5(1)	1(1)
C(24)	20(1)	29(1)	28(1)	-1(1)	0(1)	-3(1)
C(25)	20(1)	26(1)	13(1)	1(1)	2(1)	-7(1)
C(26)	14(1)	36(1)	20(1)	-4(1)	0(1)	-10(1)
C(27)	28(1)	48(1)	26(1)	-13(1)	-5(1)	-12(1)
C(28)	16(1)	22(1)	21(1)	-6(1)	0(1)	-5(1)
C(29)	25(1)	35(1)	59(1)	-21(1)	7(1)	-16(1)
C(30)	24(1)	29(1)	24(1)	-11(1)	-1(1)	0(1)
C(31)	25(1)	37(1)	23(1)	-7(1)	-5(1)	4(1)
N(1)	24(1)	14(1)	12(1)	-1(1)	-2(1)	-5(1)
N(2)	19(1)	13(1)	17(1)	2(1)	-1(1)	-6(1)
N(3)	29(1)	23(1)	14(1)	3(1)	-4(1)	-13(1)
N(4)	17(1)	26(1)	19(1)	1(1)	-3(1)	-9(1)
O(1)	27(1)	18(1)	17(1)	2(1)	-3(1)	-11(1)
O(2)	26(1)	25(1)	18(1)	1(1)	-1(1)	-14(1)
O(3)	30(1)	39(1)	24(1)	1(1)	-10(1)	-8(1)
O(4)	23(1)	35(1)	22(1)	-9(1)	-3(1)	-10(1)
S(1)	20(1)	14(1)	12(1)	-2(1)	-2(1)	-5(1)

Table A5.1.6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **5.26**-major.

atom	x	y	z	U(eq)
H(1)	4445	2436	523	23
H(3)	3997	5142	179	24
H(4)	4050	7699	-1022	27
H(5)	4166	8377	-3050	25
H(10A)	6355	1235	-2827	22
H(10B)	4349	1684	-3337	22
H(11A)	2696	1628	-1494	22
H(11B)	4371	-79	-1427	22
H(12)	944	3376	-542	30
H(14A)	-1875	3496	537	80
H(14B)	-1936	3734	1764	80

H(14C)	-1653	1981	1705	80
H(15A)	3170	1765	2104	104
H(15B)	1769	701	2634	104
H(15C)	1154	2445	2804	104
H(16A)	4116	3968	-7329	29
H(16B)	2125	5471	-7326	29
H(17A)	3159	3181	-5372	23
H(17B)	2074	5030	-5367	23
H(21)	5623	1538	-5813	29
H(22)	8139	-961	-5410	39
H(23)	10873	-1287	-4606	42
H(24)	11220	920	-4331	35
H(27A)	8507	5247	-2164	50
H(27B)	8953	6876	-2948	50
H(27C)	10679	5166	-2669	50
H(29A)	10685	-503	-565	58
H(29B)	9056	397	258	58
H(29C)	8715	845	-1078	58
H(30A)	8054	-1074	-1748	41
H(30B)	7719	-2686	-829	41
H(30C)	9868	-2617	-1207	41
H(31A)	10626	-3266	825	50
H(31B)	8586	-3558	1226	50
H(31C)	9071	-2343	1663	50
H(2)	4445	7040	-4760	21
H(3A)	4558	6712	-7948	28
H(4A)	8615	4809	-5361	26