APPLICATIONS OF CHIRAL AMIDINE CATALYSIS TOWARDS THE SYNTHESIS OF SMALL MOLECULE THERAPEUTICS AND RECENT ADVANCES IN VICINAL DIAMINE SYNTHESIS

By

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Applications of Chiral Amidine Catalysis Towards the Synthesis of Small Molecule Therapeutics and Recent Advances in Vicinal Diamine Synthesis

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Chapter 1. Enantioselective Synthesis of a GlyT1 Inhibitor

1.1 Background

Schizophrenia is among the most mysterious and costly mental disorders in terms of human suffering and social expenditure.\(^1\) This disorder, which is a severe and chronic mental illness, has prevalence estimates ranging from 0.5% to 1% of the world population.\(^2\) Though schizophrenia has traditionally been associated with mental illness alone, patients diagnosed with this disorder typically die 12 to 15 years earlier than the average population. Studies have also determined that schizophrenia causes more loss of life than most cancers and physical illnesses.\(^1\) Thus, in depth studies and potential treatments for this prevalent disorder remain of high importance.

Today, the leading treatments for this disorder are atypical antipsychotic medicines that belong to the family of dopamine D2 and serotonin 5-HT2a receptor antagonists. Although these drugs are effective in the management of symptoms such as hallucinations, paranoia, delusions, and disorganized speech and thinking, they demonstrate little effect toward improving the more negative symptoms (drowsiness, muscle spasms, blurred vision) or cognitive function. Additionally, these leading medicines have unsatisfactory side effect profiles because of their promiscuous pharmacology.\(^2\)

Due to this unsatisfactory state of the disease and treatment options, there is a need for the development of improved, safer therapeutic agents for the treatment of schizophrenia. Over the past two decades, clinical research has shown that abnormally low functioning levels of \(N\)-methyl-D-aspartate (NMDA) receptors may play a key role in the pathophysiology of schizophrenia. Restoration of NMDA receptor activity is considered a potential therapeutic avenue.\(^2\) Glycine, a common amino acid and coagonist for NMDA activation,\(^3\) has been found to potentiate the NMDA response in mouse brain neurons via an allosteric activation of the NMDA receptor.\(^4\) Though elevation of glycine levels in the brain is a pivotal finding, exogenous administration of glycine is something that must be prevented.

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1 van Os, J.; Kapur, S. *The Lancet* 2009, 374, 635-645.
Of the studies that have been conducted, one of the best preventive methods is through glycine transporter 1 (GlyT1) inhibition. GlyT1 is a type of glycine transporter that is widely expressed in glial cells throughout the nervous system.\textsuperscript{5} Research has shown that GlyT1 transporters can play a variety of roles including serving as a key novel target for the treatment of disorders such as schizophrenia.\textsuperscript{2} It has also been determined that GlyT1 inhibition can reduce allodynia and hyperalgesia in a range of chronic pain models.\textsuperscript{5} Additional studies have further confirmed that GlyT1 is essential for glycine-mediated protection of human intestinal epithelial cells against oxidative damage.\textsuperscript{6} Thus, synthesis of a desired GlyT1 target (1) is of high importance due to its potential impact on biological activity (Figure 1).

![Figure 1. Structure of GlyT1 Inhibitor 1](image)

1.2 Previously Synthesized GlyT1 Inhibitors

Previous clinical studies have demonstrated that sarcosine (N-methylglycine), a prototypical GlyT1 inhibitor, can lead to improved positive, negative, and cognitive symptoms in schizophrenic patients along with standard therapy. However, this compound cannot be classified as an optimal therapeutic agent due to its poor pharmacological profile. Thus, efforts have been made toward the development of improved sarcosine-based GlyT1 inhibitors, such as 2, 3, and 4 (Figure 2). Unfortunately, the poor pharmacological profile was sustained as these sarcosine derivatives suffered from undesirable effects including hypoactivity, ataxia (lack of muscle coordination), and reduced respiratory activity.\textsuperscript{2}

Based on these findings, a variety of pharmaceutical companies shifted their attention toward the identification and development of non-sarcosine-based GlyT1 inhibitors. Some of the successfully synthesized GlyT1 targets include a rich set of highly structurally diverse non-amino-

acid chemotypes, 5, 6, and 7, as well as a non-sarcosine-based spiropiperidine 8. Furthermore, benzoylpiperazines such as 9 and 10 were shown to be more novel chemotypes as they exhibited EC$_{50}$ potencies of 15 nM and 16 nM respectively in regards to GlyT1 inhibition via high-throughput screening (Figure 2).$^2$ Despite these improvements, the issues of a poor pharmacological profile were not resolved with these specific targets.

**Figure 2.** Previously Published GlyT1 Inhibitors

Hoffmann-La Roche has successfully synthesized and is continuing to develop a promising benzoylpiperazine chemotype. RG1678 (11) has been classified as the first potent and selective GlyT1 inhibitor to have a beneficial effect in schizophrenic patients based on a 2010 phase II clinical trial (Figure 3).$^2$
A concise synthesis of a desired GlyT1 target has been successfully completed via a collaborative effort between the laboratories of Craig W. Lindsley and Jeffrey N. Johnston at Vanderbilt University. Target molecule 1 has been identified by the Lindsley group as a potent GlyT1 inhibitor and a potential therapeutic for the treatment of schizophrenia. The more potent enantiomer of this compound was found to bind $10^4$ times better than its antipode. When examining the structure of compound 1, retrosynthetic analysis shows that a key carbon-carbon bond can be made via an asymmetric aza-Henry addition between nitroazetidine 12 and imine 13 through the use of chiral proton catalysis. Successful installation of this key carbon-carbon bond is critical as it will facilitate the development of the more potent enantiomer of GlyT1 inhibitor 1 via functional group manipulation of the scaffold (Scheme 1).

Scheme 1. Retrosynthetic Analysis of GlyT1 Inhibitor 1

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The synthesis of the desired GlyT1 inhibitor was initiated by subjecting commercially available hydroxyazetidine hydrochloride 15 to benzyl chloroformate under basic conditions in order to furnish Cbz-protected hydroxyazetidine 16 in quantitative yield. Compound 16 was then treated with triflic anhydride in the presence of pyridine to yield triflate 17 in 80% yield. Treatment of 17 with sodium iodide resulted in the expected nucleophilic substitution providing iodoazetidine 18 (88% yield), which was then treated with sodium nitrite to afford nitroazetidine 12 in modest yield (43% yield, Scheme 2).

Scheme 2. Synthesis of Nitroazetidine 12

With the desired nitroazetidine in hand, the stage was now set for the key enantioselective aza-Henry addition. This addition of azetidine 12 into Boc-protected imine 13 was to be carried out using our Brønsted basic Pyrrolidine Bis(AMidine) [PBAM] organocatalysts. Before applying the nitroazetidine motif as the nucleophile however, additions of 2-nitropropane, the simplest secondary nitroalkane, were conducted in order to examine the feasibility of this reaction system.

Additions of 2-nitropropane into imine 13 were carried out by Tyler Davis. He found that when using PBAM free base 19 as the catalyst at ambient temperature, the desired adduct (20) was obtained in 63% yield and 52% ee after a 24 hour reaction time (Scheme 3). The triflic acid salt of PBAM (19•HOTf) showed improvement as adduct 20 was furnished in comparable yield and enhanced enantioselection. This indicates that use of a polar ionic hydrogen bond is necessary in order to achieve optimal selectivity.

Scheme 3. Enantioselective 2-Nitropropane Additions
Seeing that reasonable yields and promising levels of enantioselection were achieved with 2-nitropropane, Tyler Davis then submitted nitroazetidine 12 as the donor for this reaction system. When using PBAM•HOTf as the catalyst at room temperature, he found that the desired aza-Henry adduct (14) was afforded in 86% yield and 78% ee (Scheme 4). This reaction proved to be surprisingly fast as full conversion was observed after 70 minutes. When lowering the temperature to 0 °C, increased yield and enantioselectivity was observed after a slightly prolonged reaction time of 4 hours.

Further optimization was achieved upon lowering the temperature to -20 °C. Under these chilled conditions, PBAM•HOTf provided adduct 14 in 87% yield and 86% ee over the course of 24 hours (Scheme 5). Additionally, 7-substituted PBAM catalysts were also tested with ambitions of achieving higher degrees of enantioselectivity. 7(MeO)PBAM•HOTf (19a•HOTf) proved to be ideal as the desired adduct was furnished in 93% yield and 92% ee. 7(tBu)PBAM•HOTf (19b•HOTf) was also successful, affording adduct 14 in 99% yield and 90% ee. Unfortunately when lowering the temperature to -78 °C, minimal conversion was observed after 24 hours.

With enantiomerically enriched aza-Henry adduct (14) in hand, efforts toward the desired GlyT1 target continued through the formation of a key intermediate (21) that results from a straightforward denitration. Intermediate 21 was obtained by free radical-mediated reduction by treating 14 with tributyltin hydride (tBu3SnH) and azobisisobutyronitrile (AIBN) (Scheme 6).
AIBN, which serves as a radical initiator, propagates with \(^{6}\text{Bu}_3\text{SnH}\) ultimately cleaving the nitro-carbon bond to yield 1,3-diamine 21. From this key scaffold, multiple routes could be envisioned to the desired target.

**Scheme 6. Stannane-Mediated Denitration to Key Scaffold 21**

The first route to target 1 began with cleavage of the Boc protecting group. By treating intermediate 21 with an excess of acid, the HCl salt of free amine 22 was acquired. This salt, which was carried on without further purification, was then treated with chloride 23 under basic conditions to provide 24 in 42% yield over two steps (Scheme 7).

**Scheme 7. Synthesis of Dichlorobenzamide 24 from Key Scaffold 21**

Intermediate 24 was treated with KOH in an attempt to saponify the Cbz group and subsequently decarboxylate to afford secondary amine 25. Initial attempts of this saponification using 40% KOH with varying methanol to water ratios failed to give the desired amine. Nucleophilic attack on the activated benzyl position of the Cbz group with trimethylsilyl iodide also proved fruitless. Furthermore, the use of stronger nucleophiles, such as LiOOH, did not result in the intended cleavage of the Cbz group via saponification (Scheme 8).

**Scheme 8. Saponification Attempts En Route to Amine 25**

1. 40% KOH, MeOH, 45 °C
2. TMSCl, NaI, CH$_3$CN, 55°C
3. LiOOH, MeOH-H$_2$O, THF, rt
Although these attempts did not result in the formation of the desired secondary amine (25), a notable discovery was made. When treating intermediate 24 with 40% KOH in the presence of excess methanol, two products (26 and 27) were consistently obtained. Though it was determined for compound 26 that the Cbz group was successfully cleaved, it was also evident that a methyl ester was made in lieu of the intended carbamic acid. Upon chromatographic separation and isolation of ester 26 (40% yield), an azetidine to azetidine isomerization was observed during this saponification attempt as well (Scheme 9). Support of this isomerization was confirmed by observations of desired $^3J_{HC}$ couplings through an HMBC (600 MHz) experiment (see structure elucidation, Chapter 8).

**Scheme 9. Isolated By-Products of an Attempted KOH Saponification**

**Scheme 10. Azetidine Isomerizations in Literature**

The second product isolated from this reaction, compound 27 (16% yield), also showed azetidine to azetidine isomerization. Unlike methyl ester 26 however, the Cbz group was still intact.
This isomerization was once again supported by HMBC (600 MHz) experimentation (see structure elucidation, Chapter 8).

Examples of azetidine isomerizations are known in literature. Amongst those reported include an aziridine to azetidine isomerization,\(^9\) as well as an azetidine to pyrrolidine isomerization.\(^10\) One study in particular has shown the isomerization of an azetidine ring to an oxazine ring via ring expansion\(^11\) (Scheme 10). A formation of an oxazine ring can be ruled out in our case as HMBC experimentation would result in 3 crosspeaks associated with the imine carbon of the oxazine ring. From the HMBC experimentation conducted, 3 crosspeaks were never observed for any distinct downfield carbon (Scheme 11). Though acquisition of these isomers proved to be an interesting study, the intended route toward the desired GlyT1 target (1) was unsuccessful.

### Scheme 11. Oxazine Isomer Not Observed by HMBC Experimentation

An alternative route toward the desired GlyT1 inhibitor was initiated by having intermediate 21 undergo hydrogenolysis in order to afford amine 28 via Cbz-cleavage. Treatment of this secondary amine with sulfonyl chloride 29 under basic conditions furnished the desired sulfonamide (30) in 56% isolated yield over 2 steps. Subsequent Boc deprotection and acylation with benzoyl chloride 32 afforded the desired GlyT1 target (1) in 27% yield over 2 steps (Scheme 12). HPLC analysis verified that the more potent enantiomer was present in high enantioenrichment. This was verified by observation of comparable HPLC retention times according to a patent belonging to Craig W. Lindsley and co-workers.\(^8,12\) The synthesized target was then submitted to Lindsley and colleagues to determine the potency of this compound. Tests

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\(^12\) Observed retention times can be found in the experimental section and compared to the retention times found in U.S. patent document WO 2010/114097 A1 cited above.
indicated good potency as the IC$_{50}$ value for the GlyT1 target was 800 pM. Observations of expected $^1$$J_{HC}$ couplings through an HSQC (600 MHz) experiment further confirmed the structural assignment (see structure elucidation, Chapter 8).

**Scheme 12. Successful Synthetic Route Towards Desired GlyT1 Target (−)-1**

1.4 Future Work

Future work for the GlyT1 chemistry may include the synthesis of other desired targets (i.e. derivatives) that could possibly show comparable potency to the GlyT1 target that was successfully synthesized. The same key intermediate (21) that was used to ultimately synthesize target 1 would also be used in the syntheses of these derivatives. If the syntheses of similar GlyT1 targets are pursued, it is likely that these targets could be successfully synthesized with little or no obstruction as the only major change would be the installation of different acyl groups onto scaffold 21.
Chapter 2. PBAM-Catalyzed Additions of Nitromethane into Ketimine Centers – Part I: Sulfonyl Ketimines

2.1 Background

The p53 gene is one of the most intensely investigated tumor-suppressor proteins to date. This gene, a transcription factor,\(^{13}\) is widely considered the guardian of cell division and plays a critical role in cell cycle control and apoptosis (programmed cell death). Extensive studies have shown that p53 is the most frequently mutated gene in all forms of human cancer.\(^{14}\) Hollstein and co-workers have reported that a p53 gene mutation is present among cancers of the colon, lung, esophagus, breast, liver, brain, reticuloendothelial tissues, and hemopoietic tissues.\(^{15}\) Needless to say, it is of vast importance to investigate methods of regulating the mutation of the p53 protein.

MDM2 is a protein that prevents apoptosis of cancer cells by negatively regulating the transcription factor p53.\(^{16}\) The MDM2 gene can be classified as a cellular proto-oncogene that is amplified in approximately 7% of all human cancers. Over-expression of the MDM2 protein typically occurs by enhanced transcription or translation, and when this proto-oncogene is combined with a p53 mutation, the prognosis can become much more severe.\(^{17}\) This p53-MDM2 protein–protein interaction arises when MDM2 binds directly to the p53 transactivation domain and targets p53 for proteasomal degradation.\(^{18}\) Inhibition of this protein–protein interaction can reactivate p53 and be considered as a promising approach to cancer therapy. Furthermore, small molecules could possibly serve as motifs that can sufficiently disrupt the MDM2-p53 interaction.

The Nutlins (short for Nutley inhibitors), which were identified by Vassilev and co-workers, are a class of cis-imidazoline compounds that can effectively disrupt the p53-MDM2 protein-protein interaction with median inhibitory concentration values in the 100 to 300 nM range.\(^{19}\) The development of these Nutlin compounds serves as the first potent and selective small

\(^{16}\) Doemling, A. US Patent 2011/0313167 A1
molecule inhibitors of the p53-MDM2 interaction. More specifically, the Nutlins selectively activate the p53 pathway in cells only with wild type but not mutant p53.\textsuperscript{20}

When examining the structures of the three featured Nutlin compounds (33-35), various similarities can be seen (Figure 4). Each imidazoline ring core possesses a piperazine-derived urea functionality at the 1-position along with an alkoxy-substituted aromatic ring at the 2-position. Additionally, these potent Nutlins possess halogenated aromatic rings at the 4- and 5-positions of the imidazoline as well.

![Figure 4. Structures of Nutlin Compounds 33-35](image)

Vassilev and colleagues determined that Nutlin-3 was the most potent inhibitor of the p53-MDM2 interaction. They also concluded that one enantiomer was approximately 150 times more potent than its antipode. Additional studies have shown that the more potent enantiomer, (−)-Nutlin-3 (35), has been used as a small molecule probe of cell biology and continues to be

![Scheme 13. Aza-Henry Addition en Route to (−)-Nutlin-3](image)

developed as a chemotherapeutic.\textsuperscript{21} Hoffmann-La Roche has continued extensive development of this potential anticancer compound, with RG7112 entering clinical trials in 2011.

At Vanderbilt University, an efficient asymmetric synthesis of (−)-Nutlin-3 was developed.\textsuperscript{21} The framework of this synthesis was established upon the formation of a key \textit{cis}-stilbene diamine backbone. This diamine was prepared following a PBAM-catalyzed aza-Henry addition between aryl nitroalkane 37 and aryl imine 36. \textsuperscript{6,7}(MeO)\textsubscript{2}PBAM (19c) proved to be the optimal organocatalyst for this system as adduct 38 was afforded in near-quantitative yield with high levels of enantio- and diastereoselection (Scheme 13). The masked \textit{cis}-stilbene diamine was readily converted to (−)-Nutlin-3 through a short synthetic sequence.

Other Nutlin analogs are potent inhibitors of p53-MDM2. RG7112 (39) is a dimethyl \textit{cis}-imidazoline Nutlin derivative that has been successfully synthesized and is currently being developed by Hoffmann-La Roche. Like Nutlin-3, this compound is a selective inhibitor of p53-MDM2 binding and frees p53 from negative control, activating the p53 pathway in cancer cells leading to cell cycle arrest and apoptosis.\textsuperscript{22} The enantioselective synthesis of RG7112 is of considerable interest as this molecule has shown promising results in early phases of trials in cancer patients.\textsuperscript{23}

\textbf{Figure 5.} Structural Differences Between (−)-Nutlin-3 and RG7112

Structural comparisons can be made between RG7112 and (−)-Nutlin-3 (Figure 5). Both molecules possess an imidazoline ring core with a urea functionality at the 1-position as well as aromatic substituents at the 2-, 4-, and 5-positions. The key difference between these two compounds, however, lies at the 4- and 5-positions of the imidazoline. RG7112 possesses methylated quaternary centers at these two positions while the same positions in Nutlin-3 are

methines. The presence of these quaternary centers in RG7112 (39) will ultimately change the dynamic as to how this target will be synthesized.

As previously shown, the backbone of the imidazoline entity of Nutlin-3 was readily developed through the PBAM-catalyzed enantioselective aza-Henry addition of a phenyl nitroalkane donor into a Boc-protected aldimine (Scheme 13). Yet as for RG7112, the development of the corresponding dimethyl cis-diamine backbone is more challenging. First, the use of a secondary aryl nitroalkane nucleophile is necessary. While secondary nitroalkane donors exhibited considerable success in the GlyT1 chemistry (Chapter 1), their effectiveness has been limited to additions into aldimine centers. The greater challenge of developing the desired backbone, however, is through a ketimine electrophile. While additions into aldimines can be readily achieved, additions into ketimines are more difficult since there is a greater degree of steric bulk about the electrophilic center. The increased sterics can alternate reactivity. Another known problem when handling ketimines is tautomerization into their more stable enamine form. Therefore, the use of a stable ketimine is a necessity as it allows for the possibility of achieving high-yielding aza-Henry additions as a result of minimal tautomerization. Despite these challenges, it is plausible that the dimethyl cis-diamine intermediate (40) of RG7112 can be acquired through a PBAM-catalyzed aza-Henry addition of a secondary aryl nitroalkane (41) into a methyl-derived ketimine (42) upon efficient optimization (Scheme 14).

Scheme 14. Retrosynthetic Analysis of RG7112

Before applying aryl nitroalkane 41 as the nucleophile, nitromethane was to be used in order to examine the feasibility of ketimine additions. A variety of aza-Henry additions of nitromethane into ketimine centers have been previously reported in literature (Scheme 15). Terada and colleagues demonstrated that simple organic bases, such as 1,1,3,3-tetramethylguanidine (TMG), can facilitate the addition of nitromethane into N-diphenylphosphinoyl ketimines.24

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can also promote the addition of nitromethane into $N$-thiophosphoryl ketimine centers as described by Tang.\textsuperscript{25} Despite these successes, these aza-Henry additions were not catalyzed solely by organic bases. Feng illustrated that inorganic bases, such as sodium carbonate, allow for high-yielding additions into tosyl-protected ketimines.\textsuperscript{26} Asymmetric additions of nitromethane into ketimine centers were also present in literature. Ruano has shown that nitromethane can be incorporated into $N$-sulfinyl ketimines in a diastereoselective manner when catalyzed by tetra-$n$-butylammonium fluoride (TBAF) or sodium hydroxide.\textsuperscript{27} In this same work, Ruano determined that the direction of diastereoselectivity was dependent upon which base was being used. Highly enantioselective additions into ketimine centers were reported when Feng and colleagues used a chiral $N,N'$-dioxide-copper(I) complex (43) as the catalyst.\textsuperscript{28} Here, they were able to add nitromethane into tosyl ketimines in high yield and up to 96% ee.

**Scheme 15.** Examples of Nitromethane Additions into Ketimine Centers


\textsuperscript{26} Wang, L.; Tan, C.; Liu, X.; Feng, X. Synlett \textbf{2008}, 13, 2075.


To the best of our knowledge, there is only one known example of highly enantioselective organocatalyzed aza-Henry additions into ketimines. Wang and colleagues use a simple quinine thiourea motif (44) to catalyze the addition of nitromethane as well as nitroethane and 1-nitropropane into trifluoromethyl quinazolinone centers. The corresponding dihydroquinazolinones are furnished in high yields and with excellent enantioselection (up to 98% ee). This type of aza-Henry addition is then used as a key step in the asymmetric preparation of anti-HIV drug DPC 083 (45) (Scheme 16).

Scheme 16. aza-Henry Additions into Quinazolinones en Route to DPC 083 by Wang

Our goal was then to develop highly enantioselective aza-Henry additions of primary, secondary, and tertiary nucleophiles into ketimine centers via the use of our Brønsted basic Pyrrolidine Bis(AMidine) [PBAM] organocatalysts. If these types of aza-Henry additions are readily achieved, this will lead to a much broader scope of adducts and will facilitate the ultimate goal to synthesize RG7112.

2.2 Synthesis of Sulfinyl and Sulfonyl Ketimines and Examination of Their Reactivity

Initial attempts to prepare an aryl alkyl ketimine proved to be challenging. Acquisition of a TMS-protected ketimine was of particular interest due to the easy manipulation of the silyl group. Unfortunately, multiple attempts toward synthesizing a ketimine of this type were fruitless. Despite these failures, a Cbz-protected ketimine (46) was successfully synthesized via literature

procedure in high yields and ketimine to enamine ratios (Figure 6). Attempts toward successfully installing nucleophiles as simple as nitromethane into this specific ketimine via PBAM-catalyzed aza-Henry reactions were unsuccessful as results indicated either tautomeration or hydrolysis. From these findings, it was evident that other ketimines had to be made in order to get a sense of reactivity for these aza-Henry additions.

Figure 6. Structure of Cbz-Ketimine 46 and Tautomerization to its Corresponding Enamine 47

Two ketimines that were of interest included sulfinyl ketimine 48 and tosyl ketimine 49. These ketimines, which exhibit a great degree of stability, could be readily synthesized according to the literature protocols of Ruano.31,32 Commercially available p-tolyl disulfide 50 was subjected to N-bromosuccinimide in the presence of methanol to afford sulfinate 51 quantitatively. Treatment of sulfinate 51 with lithium hexamethyldisilazide (LHMDS) gave sulfinamide 52 (48% over 2 steps), which was then condensed with acetophenone (53) furnishing sulfinyl ketimine 48 in moderate yield (60%). Subsequent oxidation of 48 with MCPBA afforded the corresponding tosyl ketimine 49 in good yield (81%) (Scheme 17).

Scheme 17. Synthesis of Sulfinyl Ketimine 48 and Tosyl Ketimine 49

In order to gain a sense of reactivity for aza-Henry additions into ketimines, literature findings were repeated. As previously mentioned, Ruano and Terada have demonstrated successful nitromethane additions via the use of simple bases such as TBAF, TMG, and sodium hydroxide

30 Ahman, J. B.; Boulton, L. T. Patent WO 2006064340
Additions into sulfinyl ketimine 48, via Ruano’s methods, were repeated using these three bases as catalysts.

Studies were initiated when sulfinyl ketimine 48 was treated with 20 mol% of TBAF in the presence of neat nitromethane. After an 18 hour reaction period, 66% conversion to adducts 54a and 54b was seen by proton NMR in a 3:1 dr (Table 1, entry 1). Raising the amount of TBAF to a full equivalent resulted in 96% conversion to 54a and 54b with minimal diastereoselectivity (entry 2). When a full equivalent of TMG was used as the catalyst in the presence of neat nitromethane, 97% conversion to the desired adducts was seen by crude NMR (entry 3). Once again, low degrees of diastereoselection were observed.

When NaOH was used as the catalyst in the presence of neat nitromethane, 4 Å molecular sieves, and a Lewis acid, 52% conversion to adducts 54a and 54b was seen in a 1:17 dr (Scheme 18). These findings, which were consistent with Ruano’s, show that a Lewis acid-mediated addition with NaOH not only reverses the direction of diastereoselectivity, it also affords the desired products in a much higher degree of selection relative to TBAF or TMG.

Ketimine additions with secondary nucleophiles proved to be problematic. Upon treating ketimine 48 with neat nitroethane in the presence of TBAF or TMG, low conversion (30%) was observed over prolonged reaction times (Scheme 19). The aza-Henry adducts 55a and 55b were
not isolated, nor were their diastereomeric ratios determined, due to low conversion and ambiguities in the crude NMR spectrum. The lack of reactivity may be due to the fact that nitroethane is more sterically hindered relative to nitromethane. This will result in a more congested system about the ketimine center upon attempted addition.

**Scheme 19. Attempted Nitroethane Additions into Ketimine 48 with TBAF and TMG**

After getting a sense of reactivity with achiral bases, additions of nitromethane into sulfinyl ketimine 48 were attempted with our chiral PBAM organocatalyst. Upon subjecting 50 mol% of PBAM free base (19) to 150 equivalents of nitromethane in the presence of THF (co-solvent), no sign of addition could be detected (Scheme 20). This could be due to the fact that PBAM may not be Brønsted basic enough to promote the nucleophilicity needed for nitromethane to effectively add into a sulfinyl ketimine center. Additionally, the catalyst binding mode with this bulkier electrophile may not be ideal as high degrees of congestion may be prevalent, thus inhibiting the desired aza-Henry addition.

**Scheme 20. Attempted Nitromethane Addition into Ketimine 48 with PBAM**

As previously seen in Scheme 18, high dr adduct (17:1) was acquired when using NaOH with a Lewis acid. In order to see if PBAM promotes addition into sulfinyl ketimine 48, an equilibrium experiment was conducted. The high dr adduct was treated with PBAM over the course of 18 hours. If starting material or a significant drop in dr was observed, it can be implied that PBAM is promoting this addition and that the equilibrium is favoring the side of the reactants. Unfortunately, when running this experiment, no drop in dr was seen reaffirming that PBAM is not making nitromethane nucleophilic enough to promote addition into the ketimine (Scheme 21).

Studies were continued by examining aza-Henry additions into tosyl ketimine 49. With a higher oxidation state, it was believed that this ketimine would be more reactive relative to sulfinyl
ketimine 48. This was tested by subjecting the tosyl ketimine to neat nitromethane in the presence of TBAF and TMG. After a 96-hour reaction time, proton NMR indicated complete conversion of starting material, as well as formation of double adduct 56 in both cases (Table 2, entries 1 and 2). When reaction times were decreased to 18 hours, the same results were obtained (entries 3 and 4). Acquisition of double adducts when using tosyl ketimine 49 versus acquisition of single adducts with sulfinyl ketimine 48 clearly indicates that the tosyl ketimine is a more reactive species as expected.

The formation of the double adduct is believed to arise from a Michael acceptor precursor (57). When nitromethane adds into the tosyl ketimine center, the desired aza-Henry adduct (58) is formed in situ. Present in the adduct, however, is a good leaving group in the tosyl amide. The two methylene protons alpha to the tosyl group are considerably acidic and can be readily deprotonated by base to cause β-elimination of the tosyl group resulting in Michael acceptor 57. This electrophilic acceptor can receive a second equivalent of nitromethane, resulting in the observed double adduct (Scheme 22).
Due to the high reactivity of tosyl ketimine 49, more hindered nucleophiles were applied in order to determine if sufficient addition could be achieved (Scheme 23). When tosyl ketimine 49 was treated with neat nitroethane in the presence of TBAF and TMG, no adduct could be detected after prolonged reaction times. aza-Henry reactions with a tertiary 2-nitropropane nucleophile were also attempted with the same bases. Once again, neither case yielded the desired adduct.

**Scheme 23. Attempted Additions of Nitroethane and 1-Nitropropane into Ketimine 49**

Despite the lack of reactivity with more hindered nitroalkanes, tosyl ketimine 49 appears to be the most reactive ketimine we have encountered up to this point when it comes to additions of nitromethane. Therefore, this ketimine was the electrophile of choice when attempting PBAM-catalyzed aza-Henry additions.

### 2.3 PBAM-Catalyzed aza-Henry Additions into Sulfonyl Ketimine Centers

With a reactive tosyl ketimine (49) in hand, PBAM-catalyzed aza-Henry additions of nitromethane could be conducted. Studies were initiated when ketimine 49 was treated with PBAM free base (19) in the presence of neat nitromethane at room temperature. After a three day reaction period, the desired aza-Henry adduct (58) was acquired in 65% isolated yield but was determined to be racemic by HPLC analysis (Table 3, entry 1). Using PBAM•HOTf (19•HOTf) as the catalyst under the same conditions, a slight increase in yield was observed as well as what appeared to be a low level of enantioselection (entry 2). PBAM•HNTf2 (19•HNTf2) proved to be a more effective catalyst as adduct 58 was furnished in 78% yield and 13% ee (entry 3). Yet when the more Brønsted basic 8(MeO)PBAM (19d) motif was applied as the catalyst, only double adduct (56) was observed (entry 4). This gives a clear indication that 8(MeO)PBAM is the most reactive organocatalyst thus far due to increased Brønsted basicity from electron-donating methoxy
substituents on the quinoline rings. Because of its high reactivity, this catalyst was carried into further studies.

With this highly reactive \(^8\)(MeO)PBAM catalyst, studies were continued to examine reactivity and possibly develop high levels of enantioselection. As previously shown, double adduct was observed upon treating ketimine 49 with 50 mol% of \(^8\)(MeO)PBAM in neat nitromethane at ambient temperature over 72 hours (Table 3, entry 4). This indicates that reaction conditions need to be modified in order to reduce the chance of β-elimination (Scheme 22) and promote the possibility of acquiring the desired single adduct (58). The most direct way of achieving this would be through reducing the catalyst loading and shortening reaction times. When the catalyst loading was reduced to 20 mol% and the reaction time was shortened to 13 hours, the desired aza-Henry adduct (58) was acquired in 47% isolated yield but with no enantioselection (Table 4, entry 1). Further decreasing the reaction time to 3.5 hours resulted in slightly enhanced yield, but no degree of enantioselection could be detected (entry 2). Significantly reducing the quantity of nucleophile to 5 and 2 equivalents in the presence of catalyst 19d at room temperature resulted in 25% and 29% isolated yields of the adduct as racemates (entries 3 and 4). Temperature studies also proved to be fruitless as lowering the temperature to -20 °C afforded the product in 17% yield and 2% ee (entry 5). When the temperature was lowered even further to -78 °C, reactivity was completely inhibited even after prolonged reaction times (entries 6 and 7). Changing the catalyst loading to 10 mol% did not show much improvement as adduct 58 was furnished in 22% yield and 7% ee over the course of 24 hours (entry 8). Lastly, the use of more dilute conditions slightly diminished yield and selection (entry 9). These studies indicate that \(^8\)(MeO)PBAM was

---

**Table 3. Catalyst Screen for Nitromethane Additions into Tosyl Ketimine 49**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conversion (%)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>77</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PBAM-HOTf</td>
<td>88</td>
<td>71</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>PBAM-HNTf</td>
<td>89</td>
<td>78</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>(^8)(MeO)PBAM</td>
<td>100</td>
<td>adduct 56</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Scheme 22**

\(R = H, PBAM (19)\)

\(R = OMe, \(^8\)(MeO)PBAM (19d)\)
not the most ideal catalyst for this reaction system as low to moderate yields of adduct were acquired with very little degree of enantioselectivity.

Table 4. Reactivity Study with $8$(MeO)PBAM

<table>
<thead>
<tr>
<th>Entry</th>
<th>MeNO$_2$ equiv</th>
<th>mol % catalyst</th>
<th>Solvent</th>
<th>$M$</th>
<th>Temp ($^\circ$C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>20</td>
<td>--</td>
<td>rt</td>
<td>13</td>
<td>47</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>20</td>
<td>--</td>
<td>rt</td>
<td>3.5</td>
<td>56</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>20</td>
<td>toluene</td>
<td>1</td>
<td>rt 14-24</td>
<td>25</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>20</td>
<td>toluene</td>
<td>1</td>
<td>rt 14-24</td>
<td>29</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>20</td>
<td>toluene</td>
<td>1</td>
<td>-20</td>
<td>14-24</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>20</td>
<td>toluene</td>
<td>1</td>
<td>-78</td>
<td>14-24</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>20</td>
<td>toluene</td>
<td>1</td>
<td>-78</td>
<td>168</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>10</td>
<td>toluene</td>
<td>1</td>
<td>rt 14-24</td>
<td>22</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>10</td>
<td>toluene</td>
<td>0.5</td>
<td>rt 14-24</td>
<td>16</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The triflimide salt of $8$(MeO)PBAM ($19$e•HNTf$_2$) was briefly examined to see if introduction of a counterion can enhance enantioselection. Upon subjecting 20 mol% of $8$(MeO)PBAM•HNTf$_2$ to ketimine $49$ in the presence of neat nitromethane at room temperature, trace amounts of product were detected by NMR after an extensive reaction period (Table 5, entry 1). When the amount of nucleophile was reduced to 20 equivalents, adduct $58$ was acquired in 33% isolated yield. Unfortunately, minimal enantioselection was observed once again (entry 2). This indicates that introduction of a salt to the Brønsted basic $8$(MeO)PBAM catalyst does not have a significant effect in regards to enantioenrichment.

Table 5. Reactivity Study with $8$(MeO)PBAM•HNTf$_2$

<table>
<thead>
<tr>
<th>Entry</th>
<th>MeNO$_2$ equiv</th>
<th>Solvent</th>
<th>$M$</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>--</td>
<td>20</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>toluene</td>
<td>1</td>
<td>33</td>
<td>4</td>
</tr>
</tbody>
</table>

The low to moderate yields of adduct acquired during the course of these runs with $8$(MeO)PBAM ($19$d) and $8$(MeO)PBAM•HNTf$_2$ ($19$d•HNTf$_2$) is mainly owed to the elimination
of the tosyl group (Scheme 22). This, of course, was due to the high Brønsted basicity of this catalyst relative to other PBAM catalysts. Control of reactivity in order to furnish high yields and minimize elimination is an optimization process that must be achieved when using this particular catalyst.

Although it appears that controlling the reactivity of this highly reactive 8(MeO)PBAM catalyst is something that needs to be resolved, enhancement of enantioselection is another area of these aza-Henry additions that needs optimization as the highest ee achieved up to this point is 13% ee (Table 3, entry 3). Since counterion control, as well as concentration, temperature, and equivalents modifications did not result in dramatic increase of enantioselection (Table 4, Table 5), efforts shifted toward making ketimines with different electronic properties in order to see if enantioselectivity is influenced by the nature of the substrate.

Two particular ketimines of interest that were made included an electron-withdrawing nosyl ketimine 59 and an electron-donating methoxy-derived ketimine 60. Simple condensations of nosyl sulfonamide 61 and para-methoxyphenyl sulfonamide 62 in the presence of acetophenone and Ti(OEt)4 furnished ketimines 59 and 60 in 7% and 21% yields respectively (Scheme 24). With these two ketimines in hand, the stage was now set to examine the difference in selectivity between electron-deficient and electron-rich electrophiles.

**Scheme 24. Synthesis of Electron-Withdrawing and Electron-Donating Ketimine Species**

![Scheme 24](image)

The catalysts to be used in this enantioselective study consisted of PBAM, PBAM•HOTf, and PBAM•HNTf2. The 8MeOPBAM catalyst could be problematic in this case because of its high reactivity and its ability to readily eliminate, especially with the highly reactive nosyl ketimine. Less reactive catalysts were purposefully chosen in order to minimize elimination so that adduct could be acquired and ee’s could be readily determined.
Before additions into more electron-deficient and electron-donating ketimines took place, aza-Henry additions into the tosyl ketimine with only 2 equivalents of nitromethane were conducted. This was to see if using 2 equivalents of nucleophile, versus 150 equivalents (Table 3), would result in a large difference in enantioselection as neat nitromethane may inhibit ideal catalyst binding.

To initiate this study, tosyl ketimine 49 was subjected to 20 mol% of PBAM in the presence of 2 equivalents of nitromethane over 96 hours at room temperature. Upon isolation, aza-Henry adduct 58 was acquired in 13% yield and 5% ee (Scheme 25). PBAM•HOTf, under the same conditions, resulted in slightly diminished yield and slightly enhanced ee. PBAM•HNTf2 was comparable to PBAM•HOTf as adduct 58 was furnished in 11% yield and 11% ee.

Scheme 25. Aza-Henry Additions into Tosyl Ketimine 49

Additions into the less reactive methoxyphenyl ketimine (60) were conducted when this electrophile was treated with 20 mol % of PBAM in the presence of 2 equivalents of nitromethane. After 96 hours, aza-Henry adduct 63 was obtained in 10% yield and 2% ee (Scheme 26). PBAM•HOTf and PBAM•HNTf2 gave identical results as adduct 63 was afforded in 27% yield and 11% ee for both cases.

Scheme 26. Aza-Henry Additions into Methoxylphenyl Ketimine 60

Additions into the more reactive nosyl ketimine 59 were more challenging since this electron deficient nosyl group is more prone to \( \beta \)-elimination. Thus, extra care had to be taken in order to obtain product so that enantioselectivity could be determined. When treating this nosyl
ketimine with only 10 mol % of PBAM in the presence of 2 equivalents of nitromethane, the desired aza-Henry adduct 64 was obtained in 25% isolated yield and 12% ee after a 24 hour reaction period (Scheme 27). PBAM•HOTf resulted in a minor improvement in yield but no change in ee. Diminished yield but slightly enhanced enantioselectivity was seen with PBAM•HNTf2 as this catalyst afforded adduct 64 in 12% yield and 15% ee. This was the highest ee observed up to this point.

Scheme 27. aza-Henry Additions into Nosyl Ketimine 59

A variety of conclusions can be drawn from this study. First, enantioselectivity does not appear to be enhanced when using 2 equivalents of the nucleophile versus 150 equivalents. The use of electron-donating substituents on the electrophile does not appear to affect selectivity as the best enantioselectivity achieved with this ketimine was 11% ee. Furthermore, incorporation of an electron-withdrawing moiety on the ketimine electrophile minimally enhances the selectivity of this system as ee values as high as 15% were obtained. Needless to say, altering the electronics of the electrophile at the para-position of the aryl ring does not appear to significantly enhance enantioselection.

2.4 Future Work

No promising degrees of enantioselection were seen for this aza-Henry system upon using a variety of PBAM catalysts and changing the electronic nature of the ketimine. Based on this lack of success, efforts now shifted toward the development of a more selective catalyst. Nagasawa and co-workers have developed guanidine-thiourea bifunctional organocatalysts that can facilitate Henry additions,33 that is the addition of nitro-nucleophiles into aldehydes. It has also been demonstrated that this addition can be done diastereoselectively.34 These catalysts became of considerable interest when Han and colleagues demonstrated that they can be used for the

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facilitation of aza-Henry addition reactions.\textsuperscript{35} The combination of these findings along with the findings of Terada in which he used tetramethylguanidine as a base, has prompted us to synthesize guanidine-derived BAM catalysts. These catalysts, when fully developed, can also be applied to aza-Henry reactions into aldimines for comparative studies. It may prove useful to examine their effectiveness in other known aza-Henry systems before applying them to ketimine additions.

\textsuperscript{35} Huang, W.; Peng, C.; Guo, L.; Hu, R.; Han, B. Synlett \textbf{2011}, \textit{20}, 2981-2984.
Chapter 3. The Guided Development of Asymmetric Mono(Amidine) Organocatalysts for the Enantioselective Synthesis of Nutlin Analogs

3.1 Background

Previously, PBAM-catalyzed aza-Henry additions into ketimine centers have proven troublesome. After exploring a variety of free-base and protonated versions of symmetric bis(amidine) catalysts for this particular system, no promising degree of enantioselection was achieved, as the highest ee obtained to this point was 15% ee. Various modifications of the ketimine electrophile, including the installation of different protecting groups as well as electronic alterations, were examined in order to improve enantioselection, but to no avail. Therefore, the next course of action to be taken would involve restructuring the current catalysts being used via installation of different functional groups.

Scheme 28. Examples of Nitromethane Additions into Aldehydes and Esters with Nagasawa’s Catalyst (65)

After investigating the literature, it was found that organocatalysts bearing guanidine and/or thiourea moieties facilitated the selective addition of nitroalkane nucleophiles into a variety of $sp^2$-hybridized centers. More specifically, Nagasawa and colleagues have shown that a guanidine-thiourea bifunctional organocatalyst (65) results in the Henry (nitroaldol) addition of nitromethane into aliphatic cyclic aldehydes and branched aliphatic aldehydes with high
enantioselection. This guanidine-thiourea catalyst also allows for highly diastereoselective Henry additions into protected α-amino- and α-hydroxy aldehydes as well as α-ketoesters while maintaining high levels of enantioselectivity (Scheme 28). When analyzing the transition states of these reactions with catalyst 65, it is proposed that the guanidine group coordinates with nitromethane through ionic interactions, while the thiourea group acts as a Brønsted acid and interacts with the aldehyde (or ester), thus lowering the LUMO energy of the carbonyl group (Figure 7). These interactions can then promote the addition of nitromethane in an enantioselective manner.

**Figure 7.** Proposed Transition State of the Guanidine-Thiourea Catalyzed Henry Reaction

The utility of this bifunctional guanidine-thiourea catalyst backbone was not limited to Henry additions of nitromethane into aldehydes and esters. After slight modifications of the catalyst structure, Nagasawa and colleagues were able to develop bifunctional catalyst 66, which readily promoted the Mannich-type reaction of aromatic α-amido sulfones with malonates, affording β-amino acid derivatives in high yields and with excellent enantioselectivity. Han and co-workers were able to expand on these findings with another derivative of Nagasawa’s catalyst. Using guanidine-thiourea motif 67, they were able facilitate the aza-Henry (or nitro-Mannich) additions of a wide array of nitroalkanes into N-Boc-protected imines, giving the desired 1,2-diamino adducts in sufficient levels of diastereoselection and high degrees of enantioselection (Scheme 29).

---

Despite the success with Nagasawa’s catalyst backbone, additional studies have shown that a bifunctional guanidine-thiourea system is not entirely necessary in order to achieve aza-Henry additions of nitroalkanes into aldimine or ketimine centers. Instead, catalysts bearing just a thiourea or guanidine entity alone have resulted in considerable success. Tang and colleagues have demonstrated that with commercially available 1,1,3,3-tetramethylguanidine (TMG), the additions of nitromethane into N-diethoxythiophosphorylimines and N-diphenylthiophosphinoylimines can

**Scheme 29. Examples of Mannich and aza-Henry Reactions with Guanidine-Thiourea Organocatalysts**

**Nagasawa**

\[
\text{Ar} - \text{HN} - \text{Boc} \quad \text{R} = \text{Bn, Me} \\
\text{Me} - \text{HN} - \text{S} \quad \text{CO}_2 \text{R} \\
\begin{array}{c}
\text{R} = \text{Bn, Me} \\
\text{10 mol \% (S,S)-66} \\
\text{toluene-H}_2\text{O} \\
\text{100 mol \% Cs}_2\text{CO}_3 \\
-10 ^\circ C \text{ to rt, 43-120 h} \\
\text{R} = \text{Bn, Me} \\
\end{array}
\]

\[
\text{Ar} - \text{N} - \text{S} \quad \text{Me} \\
\text{66} \\
\]

**Han**

\[
\text{Me} - \text{HN} - \text{Boc} \quad \text{R} = \text{Me, Bn, C}_6\text{H}_{11}, \text{CH}_2\text{OBn, (CH}_2\text{)}_2\text{OTf} \\
\text{R} = \text{Me, Bn, C}_6\text{H}_{11}, \text{CH}_2\text{OBn, (CH}_2\text{)}_2\text{OTf} \\
\begin{array}{c}
\text{5 mol \% (S,S)-67} \\
\text{toluene} \\
\text{Cs}_2\text{CO}_3 (4 \text{ equiv}) \\
0 ^\circ C \text{ to 2 h} \\
\text{R} = \text{Me, Bn, C}_6\text{H}_{11}, \text{CH}_2\text{OBn, (CH}_2\text{)}_2\text{OTf} \\
\text{Ar} = \text{CF}_3 \\
\end{array}
\]

\[
\text{67} \\
\]

**Scheme 30. Examples of aza-Henry Additions with Other Guanidine and Thiourea Catalysts**

**Tang**

\[
\text{Ar} - \text{N} \quad \text{R} = \text{Ph, OEt} \\
\begin{array}{c}
\text{10 mol \% TMG} \\
\text{CH}_3\text{NO}_2 (\text{neat}) \\
\text{rt, 0.2 to 3.5 h} \\
\text{R} = \text{Ph, OEt} \\
\text{up to 98\% yield} \\
\end{array}
\]

**Terada**

\[
\text{Ar} - \text{N} \quad \text{R} = \text{Ph, OEt} \\
\begin{array}{c}
\text{10 mol \% 68} \\
\text{CH}_3\text{NO}_2 (\text{neat}) \\
\text{rt, 5-8 d} \\
\text{up to 94\% yield, 87\% ee} \\
\end{array}
\]

**Takemoto’s Catalyst (68)**

\[
\text{Ar} - \text{N} \quad \text{R} = \text{Ph, OEt} \\
\begin{array}{c}
\text{10 mol \% TMG} \\
\text{CH}_3\text{NO}_2 (\text{neat}) \\
\text{rt, 11 to 15 h} \\
\text{up to 96\% yield} \\
\end{array}
\]
be accomplished in high yields and short reaction times. In this same work, they were also able to induce good degrees of stereoselection for the same reaction system using Takemoto’s chiral thiourea organocatalyst (68). Furthermore, Terada showed that the addition of nitromethane into diphenylphosphinoyl ketimine centers can be achieved in high yields using TMG as the catalyst (Scheme 30).

3.2 Synthetic Efforts Towards Amidine-Guanidine Asymmetric Catalysts

Based on the success in literature, we sought to restructure our traditional bis(amidine) catalyst framework in such a way that a thiourea or guanidine functionality could be incorporated. Due to the availability of various diimide species and other guanidinating reagents, the synthesis of an asymmetric bifunctional amidine-guanidine organocatalyst was the first priority (Figure 8). It was then necessary to synthesize a free amine intermediate that would readily allow for the installation of various guanidine moieties.

![Figure 8. Backbone Structure of Desired Amidine-Guanidine Catalyst](image)

In order to arrive at a key free amine intermediate, it was determined that the amidine portion of the catalyst backbone had to be developed first. This was initiated by treating resolved, enantiopure $R,R$-cyclohexane diamine (69) with phthalic anhydride (70) in the presence of para-toluene sulfonic acid monohydrate according to literature protocol. This resulted in the acid salt of phthalimide 71 in high yield (98%). Aqueous base wash of acid salt 71 would subsequently give the free base of the mono-protected diamine (72) in 84% yield. A chloro-substituted quinoline moiety was then installed via a Buchwald-Hartwig amination reaction in which amine 72 was treated with 2,4-dichloroquinoline (73) in the presence of cesium carbonate and catalytic amounts of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and bis(dibenzylideneacetone)palladium (Pd(dba)$_2$) in order to furnish amidine 74 in modest yield (42%). Phthalate deprotection with hydrazine monohydrate afforded amidine-amine species 75 in

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99% yield. This amidine-amine, which would serve as the key intermediate, can readily lead to the incorporation of a variety of guanidine derivatives as previously mentioned (Scheme 31).

**Scheme 31. Synthesis of Amidine-Amine Intermediate 75**

Initial attempts towards the installation of a guanidine entity proved to be fruitless. When key intermediate 75 was subjected to N,N'-disopropylcarbodiimide under high temperatures in the presence of a variety of solvents, no desired addition product could be isolated. When searching for alternate conditions, it was found that Shen and co-workers were able to add a wide range of aliphatic and aromatic amines into diimide centers in the presence of SmI$_2$. In this reaction pathway, it is believed that the samarium species can activate the diimide by forming a Sm(III) complex, which would promote the insertion of an amine, ultimately resulting in the formation of a desired guanidine. Unfortunately, when applying this SmI$_2$ approach to our own reaction system, no desired guanidine was obtained. Lastly, an acylation approach was attempted in which the amidine-amine intermediate (75) was treated with the HCl salt of pyrazole carboxamide (76) in the presence of THF at high temperature. Again, no sign of an amidine-guanidine moiety could be detected (Scheme 32).

Due to the lack of success of forming a guanidine functionality at this stage of the synthesis, an alternate route was proposed. Instead of trying to directly install a guanidine onto intermediate 75, we sought to subject amidine 74 to S$_N$Ar conditions in order to incorporate a pyrrolidine ring at the 4-chloro position of the quinoline ring. The incorporation of this pyrrolidine motif could possibly facilitate the formation of a guanidine species in subsequent steps. However, when

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analyzing the structure of intermediate 74, a potential problem that could arise is that the phthalate ring would be attacked and opened by pyrrolidine before the aromatic substitution reaction could take place on the quinoline. Keeping in mind this potential problem, amidine 74 was treated with pyrrolidine in the presence of trifluorotoluene under microwave conditions. Upon purification, our desired product, compound 77, was not observed. Rather, it was determined that both the substitution and the phthalate ring-opening did indeed take place, affording amidine-amide compound 78 in 80% isolated yield (Scheme 33).

Although acquired amidine-amide product 78 was not initially desired, we saw this compound as a potential enantioselective organocatalyst as a chiral pocket was present within the structure. Before this motif was applied to a ketimine reaction system, however, we wanted to test this potential amidine-amide catalyst on a previously developed aza-Henry system. The system that was chosen was the enantioselective aza-Henry addition en route to Nutlin-3, in which arylnitroalkane 37 is added into $N$-Boc protected arylimine 36, resulting in a masked cis-stilbene diamine backbone. As seen in previous studies, traditional bis(amidine) catalysts have resulted in a good degree of success for this particular system. Optimal symmetric bis(amidine) catalysts included $^6\text{MeOPBAM}$ (19d), which furnished the adduct in 99% yield, 89% ee, and 7:1 dr and $^6,7(\text{MeO})_2\text{PBAM}$ (19e), which gave the adduct in 97% yield, 91% ee, and 13:1 dr. When applying amidine-amide moiety 78, dubbed XBenzPyrrolidineAM, as the catalyst to this system, the desired adduct was obtained in 78% yield, 89% ee, and 29:1 dr (Scheme 34).
asymmetric amidine-amide catalyst subjected to this system showed comparable results with the most optimal symmetric BAM catalysts. This prompted us to further develop and investigate additional asymmetric amidine-amide organocatalysts in order to determine if this aza-Henry reaction system, en route to Nutlin-3, could be optimized to an even higher degree.

**Scheme 34. Comparative Results of the Nutlin-3 aza-Henry System**

3.3 Development of Asymmetric Amidine-Amide Organocatalysts and Their Application Towards the aza-Henry Addition en Route to Nutlin-3

Seeing that XBenzPyrrolidineAM (78) performed well compared to traditional BAM catalysts, we sought a more direct approach for the synthesis of other amidine-amide catalysts. One route to be taken would involve subjecting key amine 75 to standard amide coupling conditions followed by the installation of the pyrrolidine entity via nucleophilic aromatic substitution. An amidine-amide species that was of considerable interest, and could be readily constructed through this pathway, was a 3,5-bis(trifluoromethyl)benzamide-amidine organocatalyst (78a). This catalyst, coined 3,5( trifluoromethyl)BenzAM, can be synthesized by first treating intermediate 75 with 3,5-bis(trifluoromethyl)benzoic acid (79), EDC, and a catalytic amount of DMAP in order to afford benzamide 80a in 78% yield. A subsequent S_NAr reaction of this intermediate with pyrrolidine furnished the desired 3,5(CF3)2BenzAM motif in 69% yield (Scheme 35).

When subjecting 3,5(CF3)2BenzAM catalyst (78a) to the benchmark aza-Henry addition, we were delighted to see that higher levels of enantioselection and diastereoselection were
Scheme 35. Synthesis of $^{3,5}$(CF$_3$)$_2$BenzAM (78a)

Achieved compared to previously reported results. $^{3,5}$(CF$_3$)$_2$BenzAM gave the desired adduct in 72% yield, 96% ee, and 53:1 dr under standard reaction conditions, making this the most selective and efficient organocatalyst for the Nutlin-3 aza-Henry system up to this point (Scheme 36).

Scheme 36. Improvements on the Nutlin-3 Aza-Henry System with $^{3,5}$(CF$_3$)$_2$BenzAM (78a)

Achieving these degrees of selectivity led to the development of additional amidine-amide catalyst precursors via the amide coupling pathway. Treatment of key intermediate 75 with a series of commercially available carboxylic acids in the presence of EDC furnished a variety of desired amides in modest to good yields (45-79%). Amongst these amides were standard and substituted benzamides, naphthamides, and picolinamides (80a-80f) (Scheme 37).
Formation of these amide motifs was not limited to EDC couplings with carboxylic acids. Rather, an acylation pathway was also available with key intermediate 75. By subjecting this amine to a number of acyl chlorides under basic conditions, additional amidine-amide moieties could be obtained. This acylation approach lead to the installation of adamantyl and anthracenyl amides, pivalamides, acetamides, and other benzamides (80g-80n) (Scheme 38). Good yields (71-88%) were typically acquired throughout these acylations.

With catalyst precursors 80a-80n in hand, the stage was now set for the S_{NAr} reaction en route to the desired catalysts with pyrrolidine as the nucleophile. These reactions were conducted under microwave conditions and were typically completed within 90 minutes. A wide range in yields was observed for these substitutions as yields varied from 19% to 83% (Scheme 39).
Before applying these newly developed asymmetric amidine-amide catalysts (78a-78n) to the aza-Henry addition en route to Nutlin-3 (35), other asymmetric organocatalysts bearing functionalities other than an amide were prepared for comparative purposes. One motif that was prepared was amidine-thioamide 78o. The thioamide functionality was introduced in a straightforward manner as 3,5-(CF$_3$)$_2$BenzAM (78a) was treated with Lawesson’s reagent in order to afford the desired product (78o) in 46% yield (Scheme 40).

Another functional group that was of interest and could be readily incorporated into our catalyst backbone structure was a sulfonamide species. By treating amine 75 with commercially available 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (81) under basic conditions, we could arrive at sulfonamide precursor 80p in good yield (81%). A subsequent nucleophilic aromatic
substitution reaction of this precursor with pyrrolidine afforded the desired amidine-sulfonamide catalyst (78p) in 69% yield (Scheme 41).

**Scheme 41. Synthesis of Amidine-Sulfonamide Catalyst 78p**

Application of the newly developed amidine-amide catalyst library toward the Nutlin-3 aza-Henry system yielded interesting results in terms of reactivity and selectivity. Steric and electronic modifications of the amide functionality can lead to possible hypotheses as to how the asymmetric chiral pocket behaves for this reaction system. When the amide portion of this catalyst structure is a standard benzamide moiety (78b), the desired adduct is obtained in 71% yield, 27:1 dr, and 91% ee (Scheme 42). Although the expansion of the ring system from a benzamide to both 1- and 2-naphthamides (78c and 78e) did result in improved yields, no significant enhancement of diastereo- and enantioselection could be detected. However, when further expanding the amide portion of the catalyst to an anthracenyl amide (78j), selection was increased to a considerable degree as the desired product was isolated in 35:1 dr and 98% ee despite a slightly diminished yield (68%). This increase in enantioselection when going from a naphthamide to an anthracenyl amide indicates that sterics are an important component when it comes to creating the most selective chiral pocket for this particular reaction system.

Steric influence of these amidine-amide catalysts was not limited to solely the ring size of the amide. Higher levels of selection were also achieved via introduction of substituents at the ortho, meta, and para positions of the benzamide motif. This was reflected by the results observed with both the 2,4,6-(Me)₃benzamide- and the 3,5-(Me)₂benzamide-amidine organocatalysts (78g and 78d). These two catalysts afforded the desired aza-Henry adduct in higher yields, comparable dr’s,
and improved ee’s relative to their standard benzamide counterpart 78b, reaffirming that better enantioselection can be achieved with proper steric modification (Scheme 42).

Scheme 42. aza-Henry Results with Amidine-Amide Catalysts 78a-78n

Further comparisons can be made with catalysts 78h and 78i via electronic alterations. When introducing an electron-donating methoxy functionality at both ortho positions of the benzamide ring (catalyst 78h), diminishment in enantioselection is seen as the aza-Henry adduct is acquired in only 75% ee relative to 2,4,6(Me)3-benzamide-amide catalyst 78g, which gave the product in 94% ee. Yet, when an electron-withdrawing nitro group is incorporated at an ortho position of the ring (catalyst 78i), marginal improvement is observed as the product is afforded in 99% yield, 46:1 dr, and 84% ee (Scheme 42). Analysis of the electron-donating and electron-withdrawing benzamides presents the possibility that additional electrons/lone pairs from both the methoxy and the nitro entities may interfere with the catalyst-substrate binding, ultimately resulting in lower levels of selectivity. This possibility was further supported by the results acquired with 3,5(CF3)2BenzAM catalyst 78a, which yielded the adduct in better ee and dr (96% ee and 53:1 dr) compared to methylated counterpart 78d (95% ee and 13:1 dr). Like nitrobenzamide catalyst 78i, this catalyst (78a) possesses electron-withdrawing substituents in trifluoromethyl groups. In contrast to the nitro group however, these trifluoromethyl groups do not possess a free lone pair that can readily disrupt the catalyst binding pathway and result in less selection. Thus, it
is shown that diastereoselection and enantioselection can be slightly enhanced when electron-withdrawing character is introduced without interruption of catalyst binding.

Application of acetamide-derived amidine-amide catalysts to this aza-Henry system also showed high degrees of efficiency (Scheme 42). Pivalamide 78m, dubbed PivalAM, proved to be the most efficacious amidine-acetamide organocatalyst as this moiety provided the aza-Henry adduct in 88% yield, 45:1 dr, and 98% ee. These results signified the most optimal combination of yield, diastereoselection, and enantioselection for this reaction system up to this point. A change in electronics resulted in a considerable drop in dr and a slightly diminished ee as trichloropivalamide catalyst 78n gave the desired product in 86% yield, 9.5:1 dr, and 97% ee. Changing the electronics of the pivalamide species will alter the hydrogen bond donor ability of the amide which in turn can affect binding, causing a drop in diastereo- and enantioselection. A bulkier triphenylacetamide-amidine catalyst (78k) was also subjected to the benchmark reaction system. This catalyst fared considerably well as the adduct was obtained in 92% yield, 50:1 dr, and 94% ee. The last amidine-acetamide organocatalyst to be tested was adamantyl motif 78l. This proved to be the least sufficient amidine-acetamide catalyst as the adduct was afforded in only 90% ee despite a high yield and dr (91% yield, 43:1 dr). A drop in enantioselection from PivalAM 78m (98% ee) to adamantyl amide 78l (90% ee) reestablished the idea that optimal selectivity, especially enantioselectivity, can be achieved with the correct combination of both sterics and electronics.

A heteroaromatic picolinamide catalyst (78f) was the last amidine-amide moiety to be subjected to the Nutlin-3 aza-Henry reaction. Upon completion of addition with 78f as the catalyst, the product was acquired in 83% yield, 53:1 dr, and 75% ee (Scheme 42). Although a high yield and dr were obtained, this picolinamide-amidine catalyst displayed a lower degree of enantioselectivity relative to its standard phenyl counterpart, amidine-benzamide 78b, which furnished the adduct in 91% ee. The diminishment in enantiomeric excess when using picolinamide 78f as the catalyst can once again be attributed to the idea that an extra lone pair of electrons on the pyridine ring is readily interfering with the catalyst’s mode of binding, a trend that was observed with the methoxy- and nitrobenzamide-amidine catalysts (78h and 78i).

Two other catalyst types that were tested in this aza-Henry system included amidine-thioamide 78o and amidine-sulfonamide 78p. Thioamide catalyst 78o proved to be inefficient relative to its amide analog, \(3,5\)\((\text{CF}_3)\)\(_2\)BenzAM (78a), as the adduct was obtained in only 29% yield,
5:1 dr, and 72% ee indicating a significant decrease in yield, and a large drop in selectivity (Scheme 43). Amidine-sulfonamide motif 78p did not fare much better as this catalyst afforded the desired product in 33% yield, 26:1 dr, and 85% ee. The results obtained by 78o and 78p confirm that amidine-amide moieties give far superior degrees of reactivity and selectivity for this particular addition reaction. Changing the amide functionality to a thioamide or sulfonamide will increase the acidity of the proton on the functional group, which can once again disrupt ideal catalyst binding and result in diminished yields and selectivity.

Scheme 43. Comparative Results with Thioamide and Sulfonamide Catalysts

Previously, it was mentioned that the most optimal catalysts for the Nutlin-3 aza-Henry system, prior to the development of the amidine-amide catalyst library, were 5-MeOPBAM (19d) and 6,7-(MeO)2PBAM (19c) which gave the desired adduct in up to 13:1 dr and 91% ee. Yet when subjecting these newly developed amidine-amide catalysts to the same system, the desired product was obtained in up to 56:1 dr and 98% ee indicating a significant improvement in diastereomeric and enantioselection. The two catalysts that gave the optimal combination of yield and selectivity were 3,5-(CF3)2BenzAM (78a) and PivalAM (78m) (Figure 9). These amidine-amide motifs were used in further studies and applications as well.

Figure 9. Optimal Catalysts Chosen for Further Studies
3.4 Proposed Catalyst Binding Modes

Although the mechanistic pathway for these catalysts has not been completely studied at this point, it is evident that the combination of amidine and amide motifs allows for a fully bifunctional organocatalyst for this aza-Henry addition en route to Nutlin-3 (35). Having both the amidine and amide functionalities in the same chiral pocket can lead to a number of proposed transition states. In model A, the hydrogen of the amide can act as hydrogen bond donor to activate the N-Boc-protected imine electrophile (Figure 10). Conversely, the nitrogen of the quinoline ring serves as a Brønsted base to deprotonate the nitroalkane to form the nucleophilic nitronate. The simultaneous activation of the electrophile and generation of the nucleophile can allow for the formation of the desired masked cis-stilbene diamine adduct in a diastereo- and enantioselective fashion.

**Figure 10.** Proposed Amidine-Amide Activation and Stereochemical Model A

In another possible model, model B, the quinoline can fully deprotonate the nitroalkane, generating a positively-charged amidinium and a negatively-charged nitronate. The protons of the amidinium species can readily coordinate with the carbonyl of the Boc group and the nitrogen of the imine causing activation of the electrophile. Simultaneously, an oxygen of the nitronate, bearing a negative charge, can coordinate with the proton of the amide (Figure 11). Here, the amide can be oriented in one of two ways relative to the cyclohexyl ring. If the amide is oriented in an s-trans fashion, the substituent α to the carbonyl of the amide may be sterically repulsed by the cyclohexyl ring. However, if the amide is arranged in an s-cis manner, then the amide substituent may sterically interact with the non-coordinating oxygen of the nitronate. The varying sizes of the amide substituents, as shown in the catalyst library, can have an effect on the degree of steric repulsion. The size of the substituent may dictate if the amide will orient itself cis or trans relative to the cyclohexane ring, which may ultimately affect selectivity. Furthermore, varying the electronics of the amide entity may inductively influence the amide’s hydrogen bond donor ability.
This can affect the strength of coordination with the nitronate, which, in turn, may further influence the degrees of diastereo- and enantioselection of this addition.

**Figure 11. Proposed Amidine-Amide Activation and Stereochemical Model B**

Opposite to model B, it is also plausible that coordination between functionalities can be reversed. For a third model, model C, the quinoline once again deprotonates the nitroalkane generating an amidinium and a nitronate. Unlike the previous model however, model C proposes that the negatively-charged nitronate readily binds to both protons of the positively-charged amidinium, while the nitrogen of the imine binds to the hydrogen of the amide (Figure 12). Again, the amide functionality has the ability to orient itself in an s-cis or s-trans manner. Yet in this case, it is believed that the lowest-energy transition state will be achieved if the amide is arranged in an s-cis fashion as steric interactions should be minimized. An s-trans arrangement would be disfavored as there would be a considerable amount of steric repulsion between the amide substituent and the cyclohexyl ring as seen in model C. Once again, this model is susceptible to variations in the size and electronics of the amide motif as they can alter steric interaction and amide acidity. These variations can change the levels of selectivity of this reaction system as a consequence.

**Figure 12. Proposed Amidine-Amide Activation and Stereochemical Model C**

Lastly, model D proposes a binding pattern similar to model C, but with different charge coordination. Upon deprotonation of the nitroalkane by the quinoline, the resulting amidinium ion
can be in equilibrium with the carbonyl of the Boc-imine and generate an acidic oxonium ion. Here, the proton of the oxonium can readily coordinate with the carbonyl of the amide while the nitrogen of the imine can bind to the hydrogen of the amide. Conversely, the negatively-charged nitronate can coordinate with the lone proton of the amidine (Figure 13). If the aryl Boc-imine were to bind to the amide moiety in this proposed fashion, then it is believed that the amide would have to be in an *s*-trans orientation for easier accessibility versus an *s*-cis conformation. Forcing the amide to be in an *s*-trans arrangement in this model may once again cause steric repulsion between the amide substituent and the cyclohexyl ring. If the degree of steric repulsion was the only change taking place with varying sizes of the amide, then the ability of the amide substituent to have an effect on selectivity may be significantly reduced as this interaction is occurring outside of the chiral pocket. Furthermore, model D also hypothesizes that the aromatic portion of the imine is within the chiral pocket. As a consequence, it is possible that the sterics of the imine can have a critical influence on the selectivity of this addition. This is a potential phenomenon that needs to be examined more closely. Finally, it is also plausible that the acidity of the amide proton can change the degree of activation of the electrophile and ultimately have an effect on reactivity. Data shows that when going from an amide to a thioamide/sulfonamide species, reactivity is significantly diminished. It is feasible through this model that having an amide proton of higher acidity can cause unwanted interactions in this chiral pocket and, consequently, result in less imine activation and reactivity.

**Figure 13. Proposed Amidine-Amide Activation and Stereochemical Model D**

![Proposed Amidine-Amide Activation and Stereochemical Model D](image)

Based on the proposed transition states, it is reaffirmed that both the amidine and the amide components allow for a completely bifunctional organocatalyst system for the aza-Henry addition en route to Nutlin-3. The binding of these asymmetric catalysts is unique in the sense that unlike the traditional bis(amidine) organocatalysts, introduction of a salt is unnecessary as both Brønsted sites are present in its free base form. If a salt is indeed introduced to these amidine-amide moieties,
the lone Brønsted basic site of the quinoline will be protonated and reactivity will be lost as a result (Figure 14).

Figure 14. Deactivation of the Catalyst via Introduction of a Salt

3.5. In-Depth Analysis of Catalyst Trends

Subjection of these catalysts to the Nutlin-3 aza-Henry addition yielded data points that could be considered for potential trends. These trends mainly center upon sterics, electronics, and amide acidity.

Scheme 44. Steric Trends Observed with Asymmetric Amidine-Amide Catalysts

When examining the effects of sterics, a general trend that was observed was that an increase of amide size results in an enrichment of enantioselection. This trend was consistent among ring expansion of the amide functionality. As previous data indicates (Scheme 44), a change from a benzamide to a naphthamide does not result in an increase of enantioselection as ee is maintained at 91%. Yet when exchanging a naphthamide (78c or 78e) for an anthracenyl amide (78j), a substantial jump in selectivity is observed as this catalyst affords adduct 38 in 98% ee. This difference in enantioselectivity may revolve around the ability of the amide substituent to
rotate about the C-C sigma bond attached to the carbonyl of the amide. The rotation about this sigma bond, with asymmetric ring systems, can alter the size and shape of the chiral pocket, ultimately affecting enantioselection. When a 1- or 2-naphthyl ring is introduced as the amide substituent, two different chiral pockets can be acquired upon rotating 180° since they are non-symmetric substituents. It is plausible that the naphthamide moieties arrange themselves in such a way that they minimize their interaction in the chiral pocket as it is the lowest energy conformation (Figure 15). If the naphthamide substituents are arranged in this way, this may create a chiral environment similar to having a benzamide motif present. As a result, the degrees of enantioselection should be very similar. Yet when introducing a bulkier, symmetric anthracenyl functionality, this may change the chiral environment as the same conformation will be achieved upon rotating 180°. In other words, an anthracenyl amide does not have the ability to adapt a lower energy orientation. Part of the anthracenyl ring is forced inside creating a more shallow and narrow chiral pocket. This smaller pocket appears to be preferred for this aza-Henry system as the adduct was acquired in considerably higher ee (98% ee).

**Figure 15. Ring Expansion and its Influence on Enatoselection**

![Diagram](image)

This same phenomenon was observed upon incorporation of substituents at the ortho, meta, and para positions of benzamide catalyst 78b. As previously mentioned, installation of methyl substituents at the ortho and para positions of the benzamide ring (catalyst 78g) resulted in higher selectivity as the desired adduct was afforded in 94% ee relative to standard benzamide 78b, which gave adduct 38 in 91% ee (Scheme 44). Installation of these methyl substituents at both meta positions did not seem to make much of a difference as the adduct was acquired in 95% ee. Altering
the electronics of these methyl substituents to electron-withdrawing trifluoromethyl groups also had minimal enhancement in enantioselection as the adduct was obtained in 96% ee. What is consistent throughout these findings is that enantioselection is enhanced as steric bulk is increased via incorporation of neutral or electron-withdrawing substituents on the benzamide ring (Figure 16). The proposal made with the anthracenyl-amide catalyst (78j) also applies to the methylated benzamide catalysts. Each of the substituted benzamides are symmetric and larger compared to a standard benzamide. As the bulkier methylated benzamides rotate about the C-C sigma bond attached to the carbonyl of the amide, the same conformation will be achieved upon a 180° rotation. Like the anthracenyl amide, these methylated benzamides do not have the ability to choose a lower energy orientation. As a consequence, these methyl groups (i.e. more steric bulk) are once again forced inside creating a more shallow and narrow chiral pocket. This results in higher degrees of enantioselection relative to benzamide catalyst 78b, a very similar trend that was seen with ring expansion.

Electronic variations of the amide substituent also yielded an interesting trend. As shown in the steric trends, 3,5-(CF₃)₂BenzAM (78a), furnishes adduct 38 in 96% ee relative to standard benzamide counterpart 78b, which affords the adduct in 91% ee (Scheme 45). Although it is believed that this increase in enantioselectivity is largely due to increased steric bulk, some of it can be attributed to the electron-withdrawing character of the trifluoromethyl substituents as well. Not all electron-withdrawing motifs resulted in enhanced enantioselection, however. When introducing an electron-withdrawing nitro group at the ortho position, as shown in catalyst 78i, a drop in enantioselection was observed (84% ee). The nitro group is within proximity of the amide proton and depending on how this organocatalyst binds, it is feasible that one of the lone pairs of the nitro group is intramolecularly coordinated to the acidic proton of the amide (Figure 17). This unwanted interaction will disrupt the intended transition state in the sense that the proton of the
amide will not bind as well to the imine or nitronate. This, in turn, may inhibit activation and reactivity as well as enantioselection. This hypothesis is also supported when two electron-donating methoxy substituents are installed onto the benzamide ring. This particular catalyst ($78h$) gives the intended adduct in only 75% ee. Once again, lone pairs of electrons on these methoxy substituents may interact with the amide proton ultimately causing a diminished ee. When drawing conclusions based on these electronic alterations, it appears that electron-withdrawing groups can enrich enantioselection as long as there is no extra electronic activity (i.e. lone pairs) that can readily disrupt the ideal catalyst binding mode.

Acidity of the amide proton was another variable that lead to an interesting trend. The pK$_a$ value of the Brønsted acidic proton can vary by changing the amide substituents to other functionalities. This can lead to different degrees of reactivity and selectivity. Benzamide catalyst $78b$ possesses an amide proton with a pK$_a$ value of approximately 23 in DMSO, and when subjected to the benchmark aza-Henry addition, the desired adduct is furnished in 71% yield, 27:1 dr, and 91% ee (Scheme 46). When electron-withdrawing trifluoromethyl substituents are placed at the

**Scheme 45.** Electronic Trends Observed with Asymmetric Amidine-Amide Catalysts

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**Figure 17.** Proposed Disruptions of Binding via Unwanted Intramolecular Coordination

Acidity of the amide proton was another variable that lead to an interesting trend. The pK$_a$ value of the Brønsted acidic proton can vary by changing the amide substituents to other functionalities. This can lead to different degrees of reactivity and selectivity. Benzamide catalyst $78b$ possesses an amide proton with a pK$_a$ value of approximately 23 in DMSO, and when subjected to the benchmark aza-Henry addition, the desired adduct is furnished in 71% yield, 27:1 dr, and 91% ee (Scheme 46). When electron-withdrawing trifluoromethyl substituents are placed at the...
*meta* positions of the benzamide ring, the amide proton becomes more acidic with a pK_{a} value of 17. Though this catalyst gives similar reactivity and diastereoselection compared to benzamide 78b, enantioselection is increased to 96% ee. Once again, this jump in enantioselectivity may be a direct result of increased steric bulk. Yet, it is also possible that the increased acidity plays a role in the acquisition of this higher ee as well. Acidity of this proton was lowered even further upon the installation of thioamide and sulfonamide moieties (78o and 78p). The approximate pK_{a} values for the thioamide and sulfonamide protons were 10.5 and 9.7 respectively (DMSO scale).\(^{44,45}\) When applying these catalysts to the aza-Henry addition however, considerably lower levels of enantioselection as well as diastereoselection and reactivity were observed, indicating that these more acidic thioamide and sulfonamide protons may be inhibiting the catalyst binding mode. In other words, lesser degrees of selection and reactivity may be due to unwanted intramolecular interactions, a phenomenon previously proposed in the electronics trend. In this case however, it is possible that the Brønsted basic quinoline ring can have a high binding affinity for the proton as it becomes more and more acidic (Figure 18). This intramolecular coordination will affect the abilities of the quinoline and amide to properly bind with the imine and nitronate resulting in diminished reactivity and selectivity. In essence, it is believed that increasing the proton acidity to a pK_{a} of 17 may enhance enantioselection. Yet, if the proton is too acidic (pK_{a} ~ 10), the ideal catalyst transition state may be disrupted and optimal results will not be acquired.

\(^{44}\) Ripin, D. H.; Evans, D. A. pK_{a} Table.1 <evans.rc.fas.harvard.edu/pdf/evans_pka_table.pdf>

\(^{45}\) Bordwell pKa Table (Acidity in DMSO). <www.chem.wisc.edu/areas/reich/pkatable/index.htm>
3.6 Application of the Amidine-Amide Organocatalysts

Prior to the development of these asymmetric amidine-amide catalysts, the aza-Henry addition en route to Nutlin-3 was already optimized using symmetric BAM catalysts. According to previous studies, \(^{6,7}(\text{MeO})_2\text{PBAM}\) afforded adduct \(19c\) in 97\% yield, 13:1 dr, and 91\% ee. This enriched adduct could then be converted to (-)-Nutlin-3 (35) via a short reaction sequence (Scheme 47).

![Scheme 47. Optimization of the (-)-Nutlin-3 System](image)

However, when applying optimal BAM catalysts such as \(^{6,7}(\text{MeO})_2\text{PBAM}\) (19c) and \(8\text{MeOPBAM}\) (19d) to aza-Henry additions en route to Nutlin-3 analogs, diminished enantioselectivities were observed (60-80\% ee). Seeing that the asymmetric catalysts enhanced enatioselectivity for the Nutlin-3 aza-Henry system, we saw this as an opportunity to apply these new amidine-amide catalysts to the synthesis of Nutlin-3 derivatives (Scheme 48). To our delight, we observed that our two most optimal amidine-amide catalysts, \(^{3,5}(\text{CF})_2\text{BenzAM}\) (78a) and PivalAM (78m), furnished the new aza-Henry adducts in much higher degrees of enrichment (80-99\% ee). With the \(^{3,5}(\text{CF})_2\text{BenzAM}\) and PivalAM catalysts, a library of over 40 different aza-Henry adducts en route to Nutlin analogs were synthesized with various nitroalkanes and imines in high enantioselection.\(^{46}\) These two asymmetric catalysts tolerated aryl imines and aryl nitroalkanes possessing a number of substituents including different halogens, methyl groups, and

methoxy groups. These highly enriched adducts could then be carried onto their corresponding Nutlin derivatives via the same reaction sequence as previously reported. These analogs are then sent to St. Jude’s Children’s Research Hospital where our collaborator, Dr. Kiplin Guy, analyzes these derivatives in their binding assays. These potency studies will provide findings regarding the binding interaction with the MDM2 protein, and will guide future efforts toward developing more potent analogs.

**Scheme 48. Development of (−)-Nutlin-3 Analogs**

![Scheme 48](image)
Chapter 4. PBAM-Catalyzed Additions of Nitromethane into Ketimine Centers – Part II: Boc-Protected Trifluoromethyl Ketimines

4.1 Synthesis of a Trifluoromethyl Ketimine and Examination of its Reactivity

After seeing that electronic modifications of the tosyl protecting group did not result in promising levels of enantioselection, efforts then focused on restructuring the ketimine electrophile. When synthesizing a different ketimine however, the enhancement of reactivity and selectivity must be taken into consideration. One functional group that can readily promote reactivity and ultimately enhance enantioselectivity is a standard electron-withdrawing trifluoromethyl group.

The synthesis of a trifluoromethyl ketimine can have a number of benefits. First, this sort of ketimine will allow for a high degree of imine activation as the electron-withdrawing trifluoromethyl group is within the closest possible proximity of the electrophilic center. Secondly, if a ketimine center possessing both a trifluoromethyl group and aryl group is successfully synthesized, then the issue of tautomerization, as seen with Cbz-ketimine 46 (Figure 6), should not be of concern. In addition, the suppression of the ketimine-to-enamine tautomerization will allow for the introduction of Cbz and N-Boc protecting groups, which have, historically, allowed for the highest degrees of selection relative to any other protecting group.7,21,47,48,49,50,51,52,53,54

Furthermore, if a Boc-protected aza-Henry adduct is acquired, then β-elimination of the Boc carbamate should be minimized as the Boc carbamate is not as good of a leaving group relative to a tosyl amine. Taking these effects into account, a trifluoromethyl ketimine was of interest and could be synthesized in a straightforward manner was phenyl Boc-protected trifluoromethyl ketimine 82 (Figure 19).

Desired trifluoromethyl ketimine 82 could be readily synthesized according to literature protocols.55,56,57 Acylation of commercially available Boc anhydride (83) with hydrazine

monohydrate resulted in \textit{tert}-butyl carbazate 84 in 73% isolated yield after vacuum distillation. Treatment of this carbazate with sodium nitrite under acidic conditions will result in the corresponding azide \textit{in situ} which, upon treatment with triphenylphosphine, can be converted to iminophosphorane 85 via a Staudinger reduction (74% yield). With iminophosphorane 85 in hand, the stage was now set for an aza-Wittig reaction that would lead to the intended ketimine. When heating iminophosphorane 85 and commercially available 2,2,2-trifluoroacetophenone 86 in the presence of toluene over the course of 24 hours, ketimine 82 was furnished in modest yield upon chromatographic separation (61% yield) (Scheme 49).

\textbf{Scheme 49.} Synthesis of Boc-Protected Trifluoromethyl Ketimine 82

After successfully synthesizing ketimine 82, efforts were then shifted toward examining the reactivity of this electrophile. When treating ketimine 82 with a stoichiometric amount of 1,1,3,3-tetramethylguanidine (TMG) in neat nitromethane, we were delighted to see that this aza-Henry addition proceeded cleanly as the desired adduct (87) was afforded in 98% yield over the course of 13 hours (Scheme 50). Additionally, observation of only a single adduct indicated that the Boc protecting group was not prone to \(\beta\)-elimination under basic conditions, a phenomenon that was observed with the tosyl protecting group. With a cleaner aza-Henry reaction system and

\textbf{Scheme 50.} Examination of Reactivity with Ketimine 82
a more stable adduct, studies were now centered upon optimizing an asymmetric version of this addition with our bis(amidine) organocatalysts.

4.2 PBAM-Catalyzed Additions of Nitromethane into Trifluoromethyl Ketimine Centers

Acquisition of a manageable isolated yield was the first objective to be achieved when running this aza-Henry addition in an asymmetric fashion. This was done primarily by prolonging the reaction time and increasing the equivalents of nucleophile. When subjecting ketimine 82 to 2 equivalents of nitromethane and 50 mol% of PBAM (19) in toluene (0.1 M) at ambient temperature, minimal conversion to adduct 87 was seen after a 5 day reaction period (Scheme 51). Yet when the amount of nitromethane nucleophile was increased from 2 equivalents to 20 equivalents, the desired product was acquired in 26% isolated yield and -7% ee according to HPLC analysis. Although it is evident that more equivalents of nucleophile leads to product, no promising degree of enantioselection was observed with this new Boc-protected trifluoromethyl ketimine electrophile.

The next variable that was examined for this reaction system was the influence of added Brønsted acid. Previous studies have shown that the introduction of an acid salt to PBAM results in similar or increased levels of selectivity for a number of aza-Henry addition systems. When the triflic acid salt of PBAM (19•HOTf) was used as the catalyst for this system, adduct 87 was obtained in 31% yield and 45% ee, a considerably higher degree of enantioselectivity relative to PBAM free base (19) (Scheme 52). Upon submission of the triflimidic acid salt (PBAM•HNTf₂), the desired adduct was furnished in 38% yield and 51% ee, the highest enantioselection achieved to this point. These results show that the introduction of an acid not only reverses the direction of selectivity, it also results in a much higher level of enantioselection as well.

Additionally, one of the most optimal asymmetric amidine-amide catalysts, 3,5-(CF₃)₂BenzAM (78a), was tested in this aza-Henry system. For this particular case however, the catalyst did not fare as well as the traditional bis(amidine) catalysts as adduct 87 was acquired in
33% yield and -25% ee (Scheme 52). Needless to say, PBAM•HNTf₂ was the catalyst chosen to be carried onto further studies.

**Scheme 52. Effects of Counterions and Asymmetric Catalysts**

The effects of concentration and catalyst loading were the next two variables that were examined. Up to this point, acquisition of adduct 87 in 38% yield and 51% ee was the optimal result. This was achieved with a 50 mol% catalyst loading of PBAM•HNTf₂ and a 0.1 M concentration of toluene. When the solvent concentration was increased to 0.25 M, adduct 87 was furnished in 64% yield and 48% ee (Table 6, entry 2) indicating that increased concentrations lead to higher yields, but slightly diminished ee. Conversely, lowering the catalyst loading to 20 mol% results in a decrease in yield and a slight enhancement in selectivity as the desired adduct was afforded in 56% yield and 49% ee (entry 3). The reaction conditions used in entry 3 were carried into further studies.

**Table 6. Effects of Concentration and Catalyst Loading**

<table>
<thead>
<tr>
<th>entry</th>
<th>M</th>
<th>mol%</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>50</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>50</td>
<td>64</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>0.25</td>
<td>20</td>
<td>56</td>
<td>49</td>
</tr>
</tbody>
</table>

With a 20 mol% catalyst loading of PBAM•HNTf₂, a more in-depth solvent concentration study was conducted. When increasing the concentration of toluene from 0.25 M to 0.5 M, a decrease in both yield and enantioselection was observed (Table 7, entry 2). Further increasing the concentration to 1 M resulted in a considerable increase in yield but a continued diminishment in ee as adduct 87 was acquired in 71% yield and 42% ee (entry 3). Due to the gradual decrease in
enantioselection upon increasing the concentration, 0.25 M was still considered to be the most optimal concentration at this point.

A more in-depth nucleophile equivalence study was also conducted. Although it was previously determined that going from 2 to 20 equivalents of nitromethane resulted in isolatable yields (Scheme 51), there was still the possibility that 20 equivalents of nucleophile may not be optimal as such an excess may result in catalyst deactivation by nitroalkane binding (e.g. solvation). Therefore, lesser amounts of nucleophile were examined to see if both yield and ee could be enhanced. When dropping the amount of nitromethane from 20 equivalents to 10 equivalents, a slight increase of enantioselection was achieved. In this same run however, a considerable drop in yield was also observed (Table 7, entry 5). Dropping the equivalents further to 5 equivalents of nitromethane resulted in lower yield and no change in enantioselection as adduct 87 was furnished in 29% yield and 51% ee (entry 6). Since the minimal increase in ee cannot account for the larger loss in yield, 20 equivalents of nitromethane was still considered to be the optimal amount of nucleophile at this point.

Table 7. In-Depth Concentration and Nitromethane Equivalence Studies

<table>
<thead>
<tr>
<th>entry</th>
<th>M</th>
<th>MeNO₂ (XX equiv)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>20</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>20</td>
<td>53</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>20</td>
<td>71</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>20</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>10</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>0.25</td>
<td>5</td>
<td>29</td>
<td>51</td>
</tr>
</tbody>
</table>

*Entries 1 and 4 are the same data point

Other BAM catalysts with more Brønsted basic character were also tested to see if reactivity and selectivity could be enhanced. As previously mentioned, 8(MeO)PBAM was determined to be the most reactive catalyst for the tosyl ketimine aza-Henry system. When 8(MeO)PBAM was subjected to the trifluoromethyl ketimine aza-Henry addition, no improvement was seen as the intended product was obtained in only 42% yield and 7% ee (Scheme 53). Other available BAM catalysts of higher Brønsted basicity, such as 6(MeO)PBAM and 6,7(MeO)₂PBAM,
performed worse relative to \(^8\)(MeO)PBAM as the adduct was acquired in lower yields and minimal ee.

**Scheme 53. Application of More Brønsted Basic BAM Catalysts**

![Diagram](image)

Studies continued with the examination of additional counterions. After submitting a number of sulfonic acid salts of PBAM to the aza-Henry system, none gave superior results relative to PBAM•HNTf\(_2\) as the most optimal sulfonic acid salt, nonafluorosulfonic acid, afforded adduct 87 in 27% yield and 43% ee (Scheme 54). The bis(triflyl)methane salt (PBAM•CH\(_2\)Tf\(_2\)) appeared to be the only salt comparable to PBAM•HNTf\(_2\) as this catalyst furnished the desired product in 44% yield and 50% ee. While the lithium triflimide analog (PBAM•LiNTf\(_2\)) gave a comparable ee value relative to the triflimidic acid salt (45% ee), a significant drop in yield was observed as the adduct was obtained in only 19% yield. The bis(triflyl)methane salt, along with PBAM•HNTf\(_2\), was carried onto further studies due to similarity in catalyst behavior.

**Scheme 54. Examination of Other Counterions**

![Diagram](image)

The next variable that was altered was temperature. Traditionally, lowering the temperature results in an increase in enantioselection. This trend held true for this particular reaction system. When the reaction temperature was lowered from room temperature to 0 °C, an increase in enantioselectivity was observed at the expense of decreased yield (Table 8, entry 2). Lowering the
temperature to -20 °C had little effect on reactivity relative to 0 °C, yet higher enantioselection was observed as adduct 87 was afforded in 34% yield and 66% ee (entry 3). Unfortunately, when running this reaction at -78 °C, reactivity was inhibited as minimal conversion was seen over the course of 5 days (entry 4). However, when repeating this run at a higher concentration (0.5 M), the desired product was obtained in 6% isolated yield and 80% ee (entry 5). Although this was the highest degree of selectivity observed for this system, -20 °C was chosen as this temperature provided a more fruitful and manageable yield. Thus, the most optimal reaction conditions up to date include a 20 mol% catalyst loading of PBAM•HNTf₂, 20 equivalents of nitromethane, a 0.25 M solvent concentration, and a temperature of -20 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>temp (°C)</th>
<th>M</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>0.25</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.25</td>
<td>36</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>-20</td>
<td>0.25</td>
<td>34</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>-78</td>
<td>0.25</td>
<td>&lt;5</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>-78</td>
<td>0.5</td>
<td>6</td>
<td>80</td>
</tr>
</tbody>
</table>

Before this aza-Henry addition was conducted on a larger scale, it had to be reaffirmed that PBAM•HNTf₂, was the best catalyst under the chosen conditions, As previously shown, PBAM•CH₂Tf₂ showed comparable results at room temperature (Scheme 54). Yet when submitting the same catalyst under more chilled conditions, adduct 87 was afforded in only 20% yield and 65% ee, which proved to be inferior relative to PBAM•HNTf₂ (Scheme 55). Additionally, it had to be verified that the cyclohexane backbone of PBAM•HNTf₂ was indeed ideal. Upon subjecting a catalyst with a stilbene backbone, StilbPBAM•HNTf₂ (88•HNTf₂), to the aza-Henry

**Scheme 55. Confirmation of PBAM-HNTf₂ as the Optimal Catalyst**
system, the intended product was furnished in 15% yield and 16% ee. These results confirm that PBAM·HNTf₂ is the best catalyst for this particular reaction.

A great degree of consistency was exhibited upon scaling up this aza-Henry addition. When using 20 mg of substrate, the desired adduct is acquired in 34% yield and 66% ee. The same degree of reactivity and selectivity is seen upon a 50 fold increase of electrophile. When submitting 1 gram of the ketimine, adduct 87 is furnished in 33% yield and 66% ee (Scheme 56). This consistency indicates that the aza-Henry adduct can be taken on to its corresponding Nutlin analog in gram quantities.

**Scheme 56. Scale-Up of the Aza-Henry Addition**

4.3 Progress Towards the Synthesis of a Trifluoromethyl Ketimine Nutlin Analog

Now that the asymmetric addition of nitromethane into trifluoromethyl ketimine 82 has been developed to a degree, efforts now shifted toward the synthesis of a trifluoromethyl Nutlin derivative. The desired analog, imidazoline 89, is modified off of Nutlin-3 (35), a previously developed small molecule therapeutic. Target 89 and Nutlin-3 are similar in structure such that they both possess an imidazoline ring core with a urea functionality at the 1-position as well as aromatic substituents at the 2- and 5-positions. Key differences between the two molecules can also be seen. Target 89 possesses a trifluoromethyl quaternary center at the 5-position of the imidazoline where as the same position in Nutlin-3 is a methine. Furthermore, Nutlin-3 possesses an aromatic substituent at the 4-position, while target 89 consists of a fully saturated methylene.

**Figure 20. Structural Differences Between (−)-Nutlin-3 and Target 89**
(Figure 20). Before synthesizing compound 89 in enantioenriched form however, a synthesis was to be developed and optimized using racemic material.

It was believed that imidazoline 89 could be readily synthesized via the same reaction sequence that was developed for the synthesis of Nutin-3. After acquisition of racemic aza-Henry adduct, nitroalkane 87 was reduced to free amine 90 in near quantitative yield upon treatment with CoCl₂ and NaBH₄ in the presence of MeOH (Scheme 57). Amide coupling of amine 90 with carboxylic acid 91 in the presence of EDC and DMAP proceeded smoothly as desired amide 92 was furnished in 97% isolated yield. Treatment of 92 with trifluoroacetic acid resulted in Boc-deprotection giving the intended amine (93) in quantitative yield. From here, it was envisioned that amine 93 could be treated with CDI resulting in a reactive isocyanate in situ. This isocyanate would then be treated with 2-oxopiperazine 94 affording urea 95, which could then be taken onto imidazoline 89 via a subsequent chemoselective dehydrative cyclization reaction. Unfortunately, formation of urea 95 from tertiary amine 93 proved to be problematic.

Scheme 57. Progress Toward the Synthesis of Target 89

Amine 93 was treated with a variety of isocyanate sources under a number of reaction conditions in order to successfully develop the corresponding isocyanate in situ. Upon treating amine 93 with CDI, the isocyanate source used in the (−)-Nutlin-3 synthesis, no evidence of isocyanate formation could be detected even when heating to extreme temperatures (Table 9, entries 1 and 2). The use of triphosgene as the isocyanate source proved to be fruitless as no desired urea was formed at ambient as well as elevated temperatures (entry 3). Phosgene, the most reactive source of isocyanate, also yielded no signs of product when used both stoichiometrically and neat.
(entries 4-6). Near-quantitative recoveries of starting material throughout these attempts further support the idea that no isocyanate is being formed in situ.

Table 9. Attempts Toward Forming Urea 95 Using Various Isocyanate Sources

<table>
<thead>
<tr>
<th>entry</th>
<th>isocyanate source</th>
<th>isocyanate source equiv.</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>% recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDI</td>
<td>1.2</td>
<td>DCM/DCE</td>
<td>rt to 60</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>CDI</td>
<td>1.2</td>
<td>toluene</td>
<td>rt to 145</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>(CH₂CO₂)₂CO</td>
<td>0.4 (1.2)</td>
<td>DCM/DCE</td>
<td>rt to 90</td>
<td>92</td>
</tr>
<tr>
<td>4⁵</td>
<td>COCl₂</td>
<td>1.2</td>
<td>DCM</td>
<td>rt to 60</td>
<td>81</td>
</tr>
<tr>
<td>5⁶</td>
<td>COCl₂</td>
<td>1.2</td>
<td>DCM</td>
<td>rt to 60</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>COCl₂</td>
<td>40</td>
<td>--</td>
<td>rt to 60</td>
<td>95</td>
</tr>
</tbody>
</table>

⁵ Amine, COCl₂, DCM, DIPEA stirred at rt before addition of piperazine
⁶ Amine, COCl₂, DCM, DIPEA heated to 60 °C before addition of piperazine

The lack of isocyanate formation with these simple electrophiles may be due to poor reactivity of amine 93. The reduced reactivity can be a result of steric and electronic factors. When looking at stericas, amine 93 is a tertiary amine, which can create a high degree of congestion even when attacking an electrophile as simple as phosgene. As for electronics, this amine is within close proximity of an electron-withdrawing group. This inductive effect will reduce the basicity of the amine as a result. Therefore, measures had to be taken to increase the nucleophilicity of this amine. One direct approach would be to use bases stronger than N,N-diisopropylethylamine (DIPEA), such as DBU and LHMDS.

Scheme 58. Attempts Toward Forming Urea 95 via Isocyanate 96 with DIPEA and DBU
As previously shown, DIPEA was not sufficiently basic to promote the nucleophilicity needed to form the isocyanate in situ as starting material was consistently recovered in near-quantitative yields (Table 9). DBU, a stronger base, was also insufficient to initiate the reaction as no change by TLC analysis was detected over an extensive reaction period. In addition, starting amine was obtained in 95% recovery (Scheme 58). Yet when LHMDS was used as the base, a cyclic by-product was observed. Upon chromatographic separation, this heterocyclic by-product, identified either as cyclic urea 97a or cyclic carbamate 97b, was acquired in 22% isolated yield (Scheme 59). Although one-dimensional (1H and 13C) and two-dimensional (HSQC and HMBC) NMR techniques do not indicate a distinguishable difference between urea 97a and carbamate 97b, it is believed that the isolated by-product is the cyclic urea simply based on the increased favorability of a 5-membered ring system versus a 7-membered ring system. Furthermore, the chemical shift values observed in the 13C NMR spectrum correspond more directly with reported values of a cyclic urea versus a cyclic carbamate.58

**Scheme 59. The Use of LHMDS and Isolation of a Cyclic By-Product**

Despite what the correct structure of the cyclic by-product may be, acquisition of this heterocycle is encouraging in the sense that LHMDS is rendering amine 93 nucleophilic to promote reactivity. The proposed pathway toward the heterocyclic by-product begins with LHMDS both deprotonating the amide and activating the amine of 93. This activated amine can readily react with phosgene generating isocyanate 96 in situ. Subsequent intramolecular attack of the amide functionality into isocyanate 96 affords cyclized by-product 97a or 97b as a result (Scheme 60). This intramolecular addition will be favored over intermolecular addition of piperazine 94, hence why acyclic urea 95 was not observed in this case. At this point, conditions have not been found in which a base can promote the formation of isocyanate 96 without

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subsequent intramolecular attack of the amide moiety. With this, efforts now shifted toward treating amine 93 with available isocyanate electrophiles.

**Scheme 60. Proposed Mechanism Toward Heterocyclic By-Products**

Reacting this amine with accessible isocyanates was seen as a direct way to introduce an acyclic urea functionality. The resulting ureas from these isocyanates could then be converted into desired urea 95 upon subsequent acylation with a 2-oxopiperazine nucleophile. One readily available isocyanate source that was of interest, and may ultimately allow for the synthesis of the desired piperazine urea, was phenyl isocyanate 98.

**Table 10. Synthesis of Urea 99 and Optimization**

<table>
<thead>
<tr>
<th>entry</th>
<th>isocyanate equiv.</th>
<th>solvent</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>benzene</td>
<td>58</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>benzene</td>
<td>83</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>–</td>
<td>100</td>
<td>91</td>
</tr>
</tbody>
</table>

Phenyl isocyanate 98 proved to be a highly reactive species as sufficient conversion to urea 99 was achieved without the use of base. Upon treating amine 93 with a stoichiometric amount of
isocyanate according to literature protocol,\textsuperscript{59} 58\% conversion was seen by \textsuperscript{1}H NMR over the course of 48 hours. This led to a 45\% isolated yield of urea 99 upon chromatographic separation (Table 10, entry 1). Increasing the amount of isocyanate to 6 equivalents resulted in 83\% conversion under the same reaction conditions (entry 2). No isolated yield was reported for this run, however. Using isocyanate 98 neat (30 equiv.) proved to be most optimal as full conversion to urea 99 was seen, leading to a 91\% isolated yield (entry 3).

This addition of amine 93 into phenyl isocyanate was repeated once more with the incorporation of DBU. Here, it was believed that the presence of base will increase the nucleophilicity of the amine, which in turn would facilitate the addition and eliminate the need for excess electrophile. Based on this hypothesis, amine 93 was treated with 2 equivalents of isocyanate and 4 equivalents of DBU in the presence of benzene. Interestingly, after a 48 hour reaction period, the heterocyclic by-product (97a or 97b) was once again observed instead of the intended urea (Scheme 61). Seeing this heterocycle by \textsuperscript{1}H NMR indicates that urea 99 was formed \textit{in situ} followed by intramolecular acylation with the amide functionality. The observed acylation also shows that aniline is an efficient leaving group. This finding was beneficial as acylation attempts en route to piperazine urea 95 could be conducted using 2-oxopiperazine as the nucleophile.

\textbf{Scheme 61. Formation of a Heterocyclic By-Product via Urea 99}

![Scheme 61](image)

Acylation attempts toward desired urea 95 began when phenyl urea 99 and 2-oxopiperazine were heated to 65 °C in DCM over the course of 18 hours. This attempt proved to be fruitless as starting urea was acquired in 99\% recovery (Table 11, entry 1). The lack of conversion prompted the use of a strong base in order to enhance the nucleophilicity of piperazine 94. Therefore, the next acylation attempt involved treating the piperazine with \textit{n}-butyllithium before introducing

phenyl urea 99. After an 18 hour reaction period with DCM as the solvent, no conversion was seen by $^1$H NMR (entry 2). One potential problem that may be causing the lack of conversion is that the piperazine motif was not readily dissolving. Taking into account that this solubility issue may revolve around the solvent type, the previous reaction was repeated with THF as the solvent. Once again, the piperazine failed to dissolve resulting in no conversion to piperazine urea 95 as starting material was recovered in 91% yield (entry 3). Seeing that piperazine 94 was not soluble in both DCM and THF, it was then hypothesized that the solubility of the piperazine is substrate dependent rather than solvent dependent.

| Table 11. Failed Acylation Attempts En Route to Piperazine Urea 95 |
|---|---|---|---|---|
| entry | base | solvent | temp (°C) | % recovery |
| 1 | -- | CH$_2$Cl$_2$ | 65 | 99 |
| 2 | $^n$BuLi | CH$_2$Cl$_2$ | rt | 90 |
| 3 | $^n$BuLi | THF | rt | 91 |

Taking into consideration that piperazine solubility may be dependent on the substrate, phenyl urea 99 was carried onto its corresponding imidazoline. The chemoselective dehydrative cyclization proceeded smoothly as treatment of urea 99 with triphenylphosphine oxide and triflic anhydride afforded imidazoline 100 in 65% isolated yield over the course of 16 hours (Scheme 62). One benefit of synthesizing this imidazoline ring core is that there is no competing amide

Scheme 62. Chemoselective Dehydrative Cyclization to Imidazoline 100
functionality when it comes to a subsequent acylation attempt with 2-oxopiperazine 94. Unfortunately, imidazoline 100 proved to be unstable upon standing as decomposition was observed by $^1$H NMR. Thus, no acylations with this substrate could be attempted.

The inability to form desired piperazine urea 95 may be a direct result of insufficient electrophilicity of the phenyl urea precursor. A potential solution would be to form a more activated urea as this would facilitate the acyl substitution with the oxopiperazine nucleophile. One species that would allow for a more electrophilic urea is 4-nitrophenyl isocyanate 101, as this motif possesses an electron-withdrawing nitro group. Treatment of free amine 93 with 10 equivalents of 4-nitrophenyl isocyanate in the presence of benzene afforded the desired nitrophenyl urea (102) in 55% yield after 3 days (Scheme 63). With this more reactive nitrophenyl urea in hand, the stage was now set for subsequent acylation attempts with piperazine 94.

Scheme 63. Synthesis of Nitrophenyl Urea 102

The first acylation attempt with this new nitrophenyl urea involved heating urea 102 and piperazine 94 to 65 °C in the presence of DCM. No conversion to the desired piperazine urea was

Table 12. Failed Acylation Attempts with Nitrophenyl Urea 102

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>50-65</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>--</td>
<td>175</td>
</tr>
</tbody>
</table>
seen over an 18 hour reaction period as starting material was recovered in near-quantitative yield (Table 12, entry 1). Heating these reagents to 120 °C in the presence of toluene also resulted in no conversion (entry 2). Another acylation attempt involved heating urea 102 and piperazine 94 to 175 °C without the presence of solvent. Once again, no sign of the desired piperazine urea (95) could be detected after 18 hours (entry 3).

These failed acylation attempts with nitrophenyl urea 102 prompted us to convert this substrate to its corresponding imidazoline. Once again, the chemoselective dehydrative cyclization was successful as imidazoline 103 was furnished in 17% isolated yield after 18 hours (Scheme 64). Unfortunately, as seen with imidazoline 100, this Nutlin derivative was also prone to decomposition upon standing. Again, no acylation attempts with imidazoline 103 could be attempted.

**Scheme 64.** Chemoselective Dehydrative Cyclization to Imidazoline 103

4.4 Future Work

As previously discussed, intramolecular acylation attempts with a 2-oxopiperazine nucleophile proved to be unsuccessful even with a highly electrophilic 4-nitrophenyl urea moiety. Therefore, other measures had to be taken in order to promote the desired acylation en route to piperazine urea 95. One approach would be to further activate urea 102 via nitrosation. Nitrosations prove to be an effective method of amide activation as they can provide an electrophilic amide for hydrolysis (saponification). Evans demonstrated this in his total synthesis of vancomycin where nitrosation of a methyl amide led to a mild, late stage saponification.\(^\text{60}\) Herein, we are hoping to

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activate the nitroaniline portion of urea 102 so that intramolecular acylation with piperazine 94 can be achieved with this highly reactive electrophile (Scheme 65).

**Scheme 65. Proposed Nitrosation Route Towards the Desired Piperazine Urea**

If acylation attempts via this nitrosation method are indeed successful, the resulting urea 95 can be carried onto its corresponding Nutlin derivative (89) via a chemoselective dehydrative cyclization. Once the desired Nultin analog has been successfully synthesized with the racemate, the same synthetic route can be repeated with the enantioenriched material. This will lead us to our ultimate goal, which is to synthesize 89 as a single enantiomer.
Chapter 5. Oxidative Inter-/Intermolecular Alkene Diamination of Hydroxy Styrenes with Electron-Rich Amines via Hypervalent Iodine

5.1. Background

1,2-Diamines are ubiquitous among natural products, pharmaceutical agents, chiral ligands and bases, and other organic reagents. The biological activity associated with many of these systems and their synthetic utility has ensured that the development of new methods for the preparation of vicinal diamines is of high importance. To date, many synthetic strategies for the preparation of 1,2-diamine scaffolds have been established, facilitating access to naturally occurring vicinal diamines and those within pharmaceuticals.

Figure 21. Naturally Occurring, Non-Proteinogenic vic-Diamine Acids and Their Derivatives

In the natural world, vicinal diamines are commonly found in the form of non-proteinogenic α,β-diamino carboxylic acids. The simplest members of this group include 2,3-diaminopropionic acid (105) and 2,3-diaminobutanoic acid (106), which can be found as

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components of non-ribosomal peptide antibiotics such as bleomycin (107) (Figure 21). L-Capreomycidine (108), a key structural subunit of the tuberculostatic agent capreomycin 1B (109), has also been identified as a component of non-ribosomal peptides. Additionally, certain α,β-diamino acids are of considerable interest due to their biological role as excitatory amino acids (EAA). L-Quisqualic acid (110), isolated from the traditional Chinese medicine Shih-chun-tze, is a highly potent agonist of EAA receptors in both mammals and insects. (--)-Dysibetaine (111), isolated from the marine sponge Dysidea herbacea, is also a neuroexcitotoxin, which may bind to the glutamate receptors present in the central nervous system of mice. Other α,β-diamino acids include streptothricin F (112), an antibiotic, and nucleotide sugar UDP-2,3-diacetamido-2,3-dideoxy-D-mannuronic acid (UDP-2,3-DDMA) (113), a key building block in the biosynthesis of the lipopolysaccharide of Pseudomonas aeruginosa, an opportunistic pathogen.

Numerous alkaloid natural products are known to possess 1,2-diamine scaffolds that are associated with significant biological activity. Loline (114), a pyrrolizidine alkaloid, is known for its insecticidal activity, while the pentacyclic citrinadin A (115) exhibits cytotoxicity against murine leukemia L1210 and human epidermoid carcinoma KB cell lines (Figure 22). The vicinal diamine moiety is also present in tetrahydroisoquinoline-derived alkaloids, such as lemonomycin (116), an antitumor antibiotic. Pactamycin (117), a terrestrial alkaloid isolated from a fermentation broth of Streptomyces pactum, exhibits activity against Gram-positive and Gram-negative bacteria. In addition to terrestrial sources, marine organisms have proven to be a rich source of biologically active 1,2-diamines as well. These marine alkaloids include the antineoplastic agent agelastatin A (118), anti-tuberculosis agent manadomanzamine A (119).
and eudistomin C (120), a member of the eudistomin family that displays activity against both RNA and DNA viruses.\(^{74}\)

**Figure 22. Examples of Naturally Occurring Alkaloids That Possess the 1,2-Diamine Framework**

![Examples of Naturally Occurring Alkaloids That Possess the 1,2-Diamine Framework](image)

Vicinal diamines are also found in a wide array of pharmaceutical agents. For example, fluoroquinoline antibacterial agent moxifloxacin (121)\(^{75}\) and anticancer agent 122\(^{76}\) both possess a 1,2-diamine functionality within conformationally restricted bicyclononane ring systems (Figure 23). Target compound Sch 425078 (123), an anti-emetic agent and NK1-antagonist, contains a 1,2-diamine framework in the form of a cyclic urea.\(^{77}\) \(\alpha\)-Galactosylceramide analog HS161 (124) is a potent stimulator of invariant natural killer T cells,\(^{78}\) while sphingoid analog SG14 (125) is a specific inhibitor of human sphingosine kinase, an emerging target for cancer therapeutics.\(^{79}\) Furthermore, stilbene diamine derivative 126 has been shown to be a potent inhibitor of hepatitis C virus RNA replication,\(^{80}\) whereas *cis*-imidazoline Nutlin-3 (35) exhibits anticancer activity via

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MDM2-p53 protein-protein inhibition.\textsuperscript{81,82} Other small molecule therapeutics bearing vicinal diamines include ethambutol analog SQ109 (127), which shows potent activity against multi-drug resistant tuberculosis,\textsuperscript{83} as well as viral neuraminidase inhibitors oseltamivir (128)\textsuperscript{84} and zanamivir (129),\textsuperscript{85} which are used for the treatment of influenza A and B.

\textbf{Figure 23.} Pharmaceutically Active, Synthetic 1,2-Diamines

\begin{center}
\begin{tabular}{c}
\includegraphics[width=\textwidth]{figure23.png}
\end{tabular}
\end{center}

\begin{itemize}
\item moxifloxacin, 121
\item anticancer agent 122
\item Sch 425078, 123
\item HS161, 124
\item SG14, 125
\item stilbene diamine 126
\item nutlin-3, 35
\item SQ109, 127
\item oseltamivir, 128
\item zanamivir, 129
\end{itemize}

\subsection*{5.2. Known Methods of Alkene Diamination}

As previously mentioned, there are many known strategies for the preparation of 1,2-diamine scaffolds. The most direct and efficient means of accessing these systems is through the diamination of alkenes. Alkene diamination is an area that has been explored extensively, and as a result, can be achieved via a variety of methods.

\textsuperscript{84} Magano, J. \textit{Tetrahedron} \textbf{2011}, \textit{67}, 7875-7899.
One method of diamination involves the treatment of alkenes with binary nitrogen oxides. Jacobsen demonstrated the efficiency of these nitrogen oxides by using dinitrogen tetroxide (N$_2$O$_4$) to ultimately arrive at $C_2$-symmetric *trans*-1,2-diamine 130 (Scheme 66).$^{86}$ Here, the reaction of N$_2$O$_4$ with dimethylcyclohexene 131 under chilled conditions affords dinitro species 132 as the *trans*-diastereomer. Subsequent palladium-mediated hydrogenation of 132 yielded desired diamine 130, which was resolved by way of its mandelate salt.

Scheme 66. Jacobsen’s Synthesis of Diamine 130 via Dinitrogen Tetroxide

Wilkinson and colleagues have successfully conducted the nitronitrosylation of alkenes under medium pressure (Scheme 67).$^{87}$ This reaction was readily achieved by the disproportionation of nitric oxide (NO) to nitrous oxide (N$_2$O) and nitrogen dioxide (NO$_2$). Mechanistically, it is envisioned that this transformation proceeds through a radical pathway in which NO$_2$ adds to alkene 133, generating a $\beta$-nitro radical (134). This radical can then trap NO at 100 psi to arrive at nitronitrosylation product 135. To complement these findings, dinitrogen trioxide (N$_2$O$_3$) can be effectively employed for nitronitrosylation of alkenes as well (Scheme 67).

Scheme 67. Nitronitrosylations of Alkenes with Nitric Oxide and Dinitrogen Trioxide

This particular transformation is well documented and is compatible with a range of cyclic alkenes and dienes including dicyclopentadiene,\(^88\) cyclooctadiene,\(^89\) and indenes.\(^90\)

Alkene nitronitrosylation has also been achieved via the \textit{in situ} generation of nitrogen oxides. Demir and Findik have reported a convenient method in which silver nitrite (AgNO\(_2\)) and trimethylsilyl chloride (TMSCl) can be used for the generation of N\(_2\)O\(_3\).\(^91\) Treatment of alkenes, such as cyclohexene (133), with this AgNO\(_2\)-TMSCl combination in acetonitrile ultimately affords the desired \(\beta\)-nitroso-nitrite compounds and their corresponding dimers (Scheme 68).

\textbf{Scheme 68.} Alkene Nitronitrosylation via \textit{In Situ} Generation of N\(_2\)O\(_3\) with AgNO\(_2\)/TMSCl

Adekenov and co-workers made a serendipitous discovery in which alkene dinitration can be promoted via the combination of nitrosyl chloride and N\(_2\)O\(_4\). Although it is well known that the treatment of alkenes with nitrosyl chloride almost exclusively leads to \(\beta\)-nitroso chlorides, bisnitrination is favored when N\(_2\)O\(_4\) is present, even as a minor impurity. Adekenov demonstrated this phenomenon through the dinitration of terpenes. Upon exposure of achillin (137) to this nitrosyl chloride-nitrogen oxide system, the corresponding 1,2-dinitro compound (138) was afforded in 37\% isolated yield. Higher rates and yields (80\%) were observed with increasing amounts of N\(_2\)O\(_4\) (Scheme 69).\(^92\)

\textbf{Scheme 69.} Dinitration of Unsaturated Terpene Achillin (137) with Nitrosyl Chloride and Dinitrogen Tetroxide

Another synthesis of vicinal diamines from alkenes utilizes photochemistry, as reported by Chow.\textsuperscript{93,94,95,96} Photolysis of cyclohexene (133), in the presence of a stoichiometric amount of \textit{N}-nitrosodimethylamine, can generate \textit{trans}-addition product 139 in high yield (Scheme 70). Subsequent treatment of 139 with hyponitrous acid (HNO) furnishes nitrosohydroxylamine 140, which can then be reduced and acylated to arrive at diamine 141.

\textbf{Scheme 70.} Photoaddition of \textit{N}-Nitrosodimethylamine with Cyclohexene (133) en Route to Masked Diamine 141

\begin{center}
\includegraphics[width=\textwidth]{Scheme70.png}
\end{center}

Nitroamidation is also an efficient means for alkene dianimation. Scheinbaum illustrates this concept by reacting alkenes with nitronium tetrafluoroborate (NO$_2$BF$_4$) in acetonitrile in order to synthesize \textit{\alpha}-nitro amides.\textsuperscript{97} For example, when propene (142) is treated with NO$_2$BF$_4$, carbocation 143 is formed. Acetonitrile traps this intermediate, generating nitrilium ion 144, which undergoes hydrolysis to give the desired nitroamidation product (145), albeit in moderate yield (Scheme 71).\textsuperscript{98} Mellor and colleagues expanded on this nitroamidation method by transforming a wider range of substrates, particularly styrenes, to their corresponding nitroamides with higher yields through the use of CH$_2$Cl$_2$ as a co-solvent. Styrene (146) itself was readily converted to nitroamide 147 in 84% isolated yield.\textsuperscript{99}

\textbf{Scheme 71.} Nitroamidation of Alkenes with Nitrogen Tetrafluoroborate and Acetonitrile

\begin{center}
\includegraphics[width=\textwidth]{Scheme71.png}
\end{center}

\begin{flushleft}
\end{flushleft}
Other reagent combinations are known to promote nitroamidation of alkenes. Vankar and co-workers have developed a nitroamidation method that involves the treatment of alkenes with ceric ammonium nitrate (CAN) and sodium nitrite (NaNO₂) in acetonitrile.⁴⁰⁰ Oxidation of nitrite under these conditions generates nitrogen dioxide, which adds to cyclohexene (133), forming β-nitroalkyl radical 134. One-electron oxidation with CAN gives carbocation 148, which subsequently undergoes a Ritter reaction to give nitroamide 149. Vankar has also employed an acetyl chloride, silver nitrate (AgNO₃), and acetonitrile reagent combination for the nitroamidation of glycols and other alkenes (Scheme 72). Good yield and d.r. is demonstrated though the conversion of benzylated glycal 150 to nitroamide 151 under these reaction conditions.⁴¹

**Scheme 72. Vankar’s Alkene Nitroamidation Methods**

Iron-mediated redox chemistry has proven effective for the synthesis of 1,2-diamines, most notably through the bis-azidation of alkenes. Minisci and colleagues illustrated this phenomenon via a ferrous sulfate-mediated alkene diazidation with hydrogen peroxide (H₂O₂) as the oxidant and sodium azide (NaN₃) as the azide source (Scheme 73).⁴⁰² In a closely related approach, Minisci also reported the use of both ferrous sulfate (FeSO₄) and ferric sulfate (Fe₂(SO₄)₃) to promote the bis-azidation of more complex olefins.⁴⁰³ Steroidal compound 152, for example, was readily converted to its corresponding diazide (153) upon exposure to this Fe(II)/Fe(III) system. The efficacy of this system was improved when Galli and co-workers showed that the incorporation of ammonium peroxydisulfate ((NH₄)₂S₂O₈) resulted in increased reactivity.⁴⁰⁴ When subjected to the ferric/ferrous sulfate system in the presence of ammonium peroxydisulfate, styrene (146) was

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transformed to diazide 154 in 89% yield. This is a vast improvement compared to Minisci’s conditions, which affords 154 in only 40% yield.

Scheme 73. Ferrous Sulfate- and Ferric/Ferrous Sulfate-Mediated Diazidations of Alkenes

Fristad found that treatment of alkenes with Mn(OAc)₃ and sodium azide in acetic acid at elevated temperatures results in the formation of 1,2-diazides (Scheme 74). Snider subsequently reported a modification of Fristad’s protocol in which replacement of acetic acid with trifluoroacetic acid and acetonitrile ultimately affords the desired diazides in improved yield. This revised protocol was further extended to dihydropyran systems as their corresponding diazido compounds were furnished in good yields.

Scheme 74. Mn(III)-Mediated Diazidations of Alkenes

Heavy metal-based protocols have also been applied towards the bis-azidation of olefins. Lead(IV) acetate azide ([Pb(OAc)_{4-n}(N_3)_n]), which is generated by the reaction of lead(IV) acetate and trimethylsilyl azide (TMSN_3), has proven to be an effective azide transfer reagent. Zbiral demonstrates this by reacting lead(IV) acetate azide with alkenes in acetonitrile at 20 °C to arrive at vicinal diazides (Scheme 75). More specifically, [Pb(OAc)_{4-n}(N_3)_n] readily converts styrene (146) to diazide 154 in 70% isolated yield. While Zbiral has shown the usefulness of lead(IV) acetate azide with acyclic olefins, Draper reported that this same reagent can be used for the transformation of cyclic alkenes to 1,2-diazides as well. For example, when steroidal dienone 159 is treated with lead(IV) acetate azide, diazido compound 160 can be afforded in 61% yield.

![Scheme 75. Reaction of [Pb(OAc)_{4-n}(N_3)_n] with Acyclic and Cyclic Olefins](image)

Closely related to lead(IV) acetate azide, thallium(III) acetate azide ([Tl(OAc)_{3-n}(N_3)_n]) can also be employed for alkene bis-azidation. Like its lead analog, thallium(III) acetate azide is prepared by reacting thallium(III) acetate with TMSN_3. Application of this particular azide transfer reagent by Zbiral was fruitful as both cyclic and acyclic alkenes could be converted to their desired vicinal diazides (Scheme 76). Cyclohexene (133) and 4-allylanisole (161) were transformed into their corresponding aziridinylazothallium compounds (162 and 163), upon exposure to thallium(III) acetate azide. Subsequent thermolysis of 162 and 163 resulted in the formation of diazido compounds 164 and 165 in 38% and 30% yields respectively.

Aside from alkene diazidation, heavy metal protocols have been used for the direct diamination of alkenes as well. Barluenga has reported an efficient method for olefin diamination.

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using thallium(III) acetate (Scheme 77). This is exemplified through the transformation of cyclohexene (133) to diamine (166). Cyclohexene, when subjected to aniline and Tl(OAc)_3, is thought to proceed through aminothallation en route to organothallium intermediate 167. Substitution of the thallium entity via an S_N1 pathway with another equivalent of aniline yields the desired diamine (166) in high yield.

**Scheme 77.** Barluenga’s Addition of Aromatic Amines to Alkenes in the Presence of Thallium(III) Acetate

In addition to thallium, mercury(II)-mediated protocols can be used for the synthesis of vicinal diamines. Barluenga has demonstrated that mercury(II) reagents, most notably mercury(II) tetrafluoroborate (HgO•2HBF_4), can undergo alkene aminomercuration to form β-amino alkylmercury(II) salts (Scheme 78). Substitution of the mercury moiety with nucleophilic amine generates the desired diamine. Like thallium-mediated diaminations, primary and secondary amines are tolerated with mercury(II).

**Scheme 78.** Barluenga’s Addition of Aromatic Amines to Alkenes in the Presence of Mercury(II) Tetrafluoroborate

Transition metal catalysis can be classified as the most extensively explored and dominant area of chemistry when it comes to the dianimation of olefins. Numerous transition metals have been applied towards the synthesis of vicinal diamines including cobalt, ruthenium, osmium,

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palladium, nickel, copper, and gold. With these possibilities, transition metal catalysis can achieve alkene diamination to a high degree of generality.

The use of metal nitrosyl complexes are amongst the earliest applications of transition metals en route to diamination. Brunner and Loskot report a ligand-based reaction of cobalt nitrosyl complex 169 with bicyclo[2.2.1]hept-2-enes.112 This nitrosyl complex, which is generated from the reaction of cyclopentadienylnicotinoyl dicyanomethylene (170) and nitric oxide, can undergo addition to strained alkenes to form cobalt dinitrosoalkane complexes. Good reactivity is demonstrated as nitrosyl complex 169 readily converts norbornene (171) to dinitrosoalkane complex 172 in 90% isolated yield (Scheme 79). This process is diastereoselective as only the exo compounds are formed. Bergman improved on Brunner’s and Loskot’s findings by using cobalt dinitrosoalkane complexes as intermediates in order to access free 1,2-diamines.113 In this study, in situ reduction of dinitrosoalkane ligands with LiAlH₄ affords the corresponding unmasked diamines in good yield and with high levels of diastereoselection.

Scheme 79. Diaminations of Alkenes Using CyclopentadienylNitrosylcobalt Dimer 169

In 2011, Bergman and Toste reported ruthenium-mediated alkene bis-nitrosylations as well.114 Here, treatment of (cymene)ruthenium dichloride dimer (174) with nitric oxide in THF generates dinitroso complex 175 (Scheme 80). This complex can readily react with strained alkenes in the presence of chelating ligands to arrive at six-coordinate, ruthenium-based dinitrosoalkane complexes.

113 (a) Becker, P. N.; White, M. A.; Bergman, R. G. J. Am. Chem. Soc. 1980, 102, 5676-5677; (b) Becker, P. N.; Bergman, R. G. Organometallics 1983, 2, 787-796.
Imidoosmium(VIII) reagents have also proven effective in the field of alkene diamination. Sharpless and colleagues were the first to report the use of tris(tert-butylimido)osmium (177) to promote diaminations of terminal and trans-disubstituted alkenes.\(^{115}\) To illustrate, styrene (146) and dimethyl fumarate (178) were transformed to their osmium-derived diimido complexes (179 and 180) upon exposure to imidoosmium 177 (Scheme 81). These complexes can be reduced to their corresponding 1,2-di-tert-butylamines (181 and 182) when treated with LiAlH₄. Additionally, Schrock and co-workers employed a more sterically encumbered aryl trisimidoosmium complex (183) for the synthesis of masked vicinal diamines.\(^{116}\) This complex proved fruitful as simple alkenes such as ethylene (184) and norbornene (171) were converted to metallaimidazolidines 185 and 186 in 78% and 46% yields.

Scheme 80. Reaction of Alkenes with Dinitrosyl Complex 175

Scheme 81. Stoichiometric Diamination of Alkenes with Imidoosmium(VIII) Complexes


Muñiz and colleagues expanded on the studies of Sharpless and Schrock by deploying strategies that effectively control the absolute facial selectivity of imidoosmium(VIII)-mediated diaminations. One approach in particular involves the use of chiral auxiliaries in order to achieve alkene diamination in a diastereoselective fashion. This is exemplified as reactions of electron-deficient (−)-8-phenylmenthyl acrylate derivatives (187) with imidoosmium 188 proceed through the Re-face, furnishing masked diamines (189) with high levels of diastereoselection (Scheme 82). An enantioselective catalytic variant has also been developed, which employs a Ti-TADDOLate catalyst and imidoosmium 188 as the stoichiometric nitrogen source. Under these conditions, electron-deficient crotonyl oxazolidinones (190) are readily converted to their osmium-derived 1,2-diamines (191) with good to excellent levels of enantioselection.

Scheme 82. Diastereo- and Enantioselective Diaminations with Imidoosmium 188

Palladium is one of the more broadly effective transition metals when it comes to the diamination of olefins. The first palladium-assisted alkene diamination was reported in 1978 by Bäckvall. Here, stoichiometric quantities of trans-bis(benzonitrile)dichloropalladium(II) are used to promote the synthesis of vicinal diamines from simple 1,2-disubstituted alkenes. Hex-3-ene (192), for example, undergoes trans-aminopalladation to amino alkylpalladium(II) species 193 upon exposure to the stoichiometric palladium and dimethylamine (Scheme 83). Oxidation of 193 with MCPBA gives a palladium(IV) species, which is reductively displaced by another equivalent of dimethylamine, ultimately affording diamine 194 in 45% yield with high syn-selectivity.

Although Bäckvall’s stoichiometric diamination showed great promise for the advancement of palladium-mediated protocols, catalytic versions of this process were not discovered until 2005 when Booker-Milburn and co-workers reported the first palladium(II)-catalyzed intermolecular diamination of alkenes. They found that treatment of 1,3-dienes, such as isoprene, with N,N’-diethylurea (195) in the presence of catalytic bis(acetonitrile)palladium dichloride and benzoquinone led to the formation of cyclic ureas 196 and 197 in 81% yield with a 77:23 regioisomer ratio (Scheme 84). Furthermore, Muñiz and colleagues demonstrated the first palladium(II)-catalyzed intramolecular alkene diamination with alkenyl-substituted ureas (198). When subjected to catalytic palladium(II) acetate and stoichiometric quantities of hypervalent iodine oxidant (PhI(OAc)2) under basic conditions, these terminal alkenes were transformed to their desired cyclic ureas (199) with five-, six-, and seven-membered fused rings in excellent yield.

In addition to terminal alkenes, Muñiz has shown that palladium(II)-catalyzed intramolecular diaminations can also be achieved with internal alkenes. Upon exposure to the palladium(II)acetate-phenyl iodine diacetate (Pd(OAc)2-PhI(OAc)2) combination in the presence of base, homoallylic sulfonamide 200 readily undergoes double annulation to afford bis(indoline)
201 in 89% isolated yield (Scheme 85). Aliphatic- and naphthyl-derived homoallylic sulfonamides are tolerated in this reaction as well.

**Scheme 85. Muñiz’s Pd(II)-Catalyzed Intramolecular Diamination of Internal Alkenes en Route to Bis(indolines)**

![Scheme 85](image)

Another notable advancement by Muñiz in the area of palladium-catalyzed alkene diamination is the incorporation of copper(II) salts as terminal oxidants. One system in which this palladium-copper catalyst-oxidant combination can be effectively employed is through the intramolecular cycloguanidation of terminal alkenes (Scheme 86).123 With Pd(OAc)$_2$ as the catalyst and CuCl$_2$ as the terminal oxidant, N-alkenyl guanidines (202) can be converted to their respective Boc- or Cbz- protected bicyclic guanidines (203) in up to 99% yield.

**Scheme 86. Pd(II)-Catalyzed Intramolecular Cycloguanidation of Alkenes with Copper Chloride as the Oxidant**

![Scheme 86](image)

In an extension of their work on the intramolecular diamination of tethered ureas, Muñiz and colleagues have developed a doubly intermolecular variant of their methodology. This particular method features the regioselective transfer of nitrogen from two distinct sources in bis(tosylimide) and saccharin (Scheme 87).124 For example, when using bis(benzonitrile)palladium dichloride as the precatalyst and iodosobenzene dipivalate as the oxidant, vinyl cyclohexane (204) can undergo addition to afford heterodiamine 205 in 78% isolated yield with complete regioselectivity.

**Scheme 87. Doubly Intermolecular Pd(II)-Catalyzed Diamination of Terminal Alkenes**

![Scheme 87](image)

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Complementary to Muñiz’s doubly intermolecular protocol, Michael and co-workers have reported the intra/intermolecular diamination of terminal alkenyl amides, carbamates, and ureas (Scheme 88).

Here, N-fluoro-bis(phenylsulfonyl)imide (NFBS) is used as an external electrophilic aminating agent. When treated with NFBS, catalytic palladium(II) trifluoroacetate and a triethylammonium benzenesulfonamide additive, these terminal alkenes (206) readily undergo cyclization en route to their 2-aminomethyl pyrrolidine derivatives (207) in moderate to good yield. This methodology by Michael is beneficial not only for its generality and functional/protecting group tolerance, but because these diamination products can be differentially deprotected under mild conditions as well.

Scheme 88. NFBS-Promoted Intra/Intermolecular Diamination of Terminal Alkenes

Nickel catalysis has also been used as a means for alkene diamination. Muñiz and colleagues demonstrate the efficacy of nickel(II) salts in the intramolecular diamination of N-alkenyl sulfamides, ureas, and guanidines (Scheme 89).

Upon exposure to catalytic nickel(II) and phenyliodine diacetate (PhI(OAc)$_2$) in the presence of base, these terminal alkenes (208) are transformed to their corresponding diamines (209) in up to 94% yield and with a high degree of generality.

Scheme 89. Nickel(II)-Catalyzed Intramolecular Alkene Diamination

Chemler and co-workers have pioneered the use of copper(II) carboxylates for the diamination of olefins. In 2005, this group successfully employed copper(II) acetate to promote the intramolecular diamination of γ-alkenyl and δ-alkenyl-substituted sulfamides (Scheme 90).

To illustrate, alkenyl sulfamide 210 undergoes cyclization to afford its corresponding 5-membered

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cyclic sulfamide (211) when subjected to stoichiometric quantities of copper(II) acetate under basic conditions. Additionally, δ-alkenyl-substituted sulfamides were smoothly converted to their 6-membered cyclic sulfamides under identical reaction parameters.

**Scheme 90.** Chemler’s Intramolecular Diamination of Alkenyl-Substituted Sulfamides with Copper(II) Acetate

\[
\begin{array}{c}
\text{Me} \quad \text{Me} \\
\text{NH} \quad \text{O}_2\text{S} \quad \text{NH}_{\text{Bn}} \\
\text{Cu(OAc)}_2 (3 \text{ equiv}) \quad \text{K}_2\text{CO}_3 (2 \text{ equiv}) \\
\text{DMSO (10 equiv), DMF} 90-120^\circ \text{C, 48 h} \quad (73\%) \\
\end{array}
\]

Although copper(II) acetate has proven effective for the intramolecular diamination of alkenyl sulfamides, this particular species does suffer from a low degree of solubility, resulting in methodological limitations. As a result, Chemler has introduced copper(II) neodecanoate ([Cu(nd)\(_2\)]) as a second-generation mediator for the diamination of alkenes.\(^{128}\) When exposing this copper(II) carboxylate to γ-alkenyl-substituted sulfamide 212 in the presence of base at elevated temperatures, the desired cyclic sulfamide (213) is furnished in 65% isolated yield as a single diastereomer (Scheme 91). It is also worthy to note that these revised conditions facilitate the generation of a broader ranges of bis( amino) products including ureas, bis(anilines), and α-amidopyrroles.

**Scheme 91.** Chemler’s Copper(II) Neodecanoate-Promoted Intramolecular Diamination of Terminal Alkenes

\[
\begin{array}{c}
\text{Me} \quad \text{Me} \\
\text{O}_2\text{S} \quad \text{NH}_{\text{Bn}} \\
\text{Cu(nd)\(_2\)} (3 \text{ equiv}) \quad \text{K}_2\text{CO}_3 (2 \text{ equiv}) \\
\text{DCE, 120 }^\circ \text{C, 48 h} \quad \text{pressure tube} \quad (85\% \text{ d. r. } \sim >20:1) \\
\end{array}
\]

In 2010, Chemler and colleagues expanded on their original diamination methodology by reporting an intra/intermolecular variation that involves external nucleophiles such as azide, sulfonamides, benzamides, and anilines.\(^ {129}\) This particular study employs copper(II) 2-ethylhexanoate ([Cu(eh)\(_2\)]) to facilitate the diamination of 2-substituted 1-allyl-1-benzyl ureas (214) (Scheme 92). Once the urea functionality undergoes intramolecular ring closure on the alkene, intermolecular nucleophilic attack by an external amino source generates the second C-N bond ultimately affording 4-substituted imidazolinones (215).


Chemler took this intra/intermolecular approach one step further by achieving a variant with promising levels of enantioselection. Here, chiral bis(oxazoline) ligand 216 is used in conjunction with catalytic copper(II) triflate and MnO₂ as the terminal oxidant to promote the enantioselective intra/intermolecular diamination of mesyl-protected allylaniline 217 (Scheme 93). With electron-deficient bis(tosylimide) as the external amino source, masked diamine 218 is acquired in 64% yield and 71% ee under these reaction conditions.

Recently, Wang and Shen reported a copper-catalyzed intra/intermolecular diamination of unactivated alkenes with hydroxylamines. These hydroxyl amines are novel in this study as they serve as a source of electron-rich amines. The efficacy of this system is demonstrated through the direct conversion of alkenyl amides to amino-substituted lactams. For example, when unsaturated amide 219 is treated with O-benzoyl hydroxymorpholine (220) in the presence of catalytic copper(II) acetate, morpholine-substituted lactam 221 is furnished in 80% yield (Scheme 94). Other cyclic and aliphatic secondary amines are tolerated in this reaction system as well.

Gold catalysis has also proven to be an effective avenue towards alkene diamination. In 2009, Muñiz and co-workers reported the use of gold(I) to facilitate the doubly intramolecular diamination of alkenyl-derived ureas. When subjecting triphenylphosphine gold(I) acetate as

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the catalyst and PhI(OAc)₂ as the oxidant, N-γ-alkenyl ureas (222) can readily convert to their corresponding bicyclic imidazolinones (223) in high yield (Scheme 95).

**Scheme 95.** Gold-Catalyzed Intramolecular Diamination of N-γ-Alkenyl-Substituted Ureas

![Scheme 95](image)

To complement Muñiz’s doubly intramolecular protocol, Nevado and de Haro have reported a gold-catalyzed intra/intermolecular diamination of N-γ-alkenyl tosylated amines (224). When using cationic complex [(Ph₃P)AuSbF₆] as the catalyst and Selectfluor (225) as an oxidant, these alkenyl tosylated amines undergo a 6-endo-trig cyclization that traps a nitrile solvent. Subsequent in situ hydrolysis of the nitrile moiety ultimately results in the generation of N-piperidin-3-yl carboxamides (226) in moderate to good yield (Scheme 96).

**Scheme 96.** Gold-Catalyzed Oxidative Intra/Intermolecular Diamination of N-γ-Alkenyl Tosylated Amines

![Scheme 96](image)

Shi and co-workers have extensively explored the use of strained diaziridinones and their analogs as versatile nitrogen sources for metal-mediated alkene dianimations. In 2007, Shi first reported the use of di-tert-butyldiaziridinone (227) as a nitrogen source in the diamination of conjugated dienes (228). Treatment of these dienes with 227 and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) at elevated temperatures results in the formation of

**Scheme 97.** Symmetric and Asymmetric Pd-Catalyzed Diaminations of Dienes with Di-tert-Butyldiaziridinone

![Scheme 97](image)

imidazolidinones (229) in high yield and with excellent regioselectivity (Scheme 97). Shortly thereafter, the same group reported a highly efficacious enantioselective variant of this methodology by employing Pd$_2$(dba)$_3$ as the palladium(0) source and BINOL-based phosphorous amidite 232 as the chiral ligand.\textsuperscript{134}

In addition to dienes, Shi has also found that monosubstituted and 1,1-disubstituted olefins undergo palladium(0)-catalyzed dehydrogenative diamination at the allylic and homoallylic positions in the presence of excess di-tert-butylidiaziridinone (227).\textsuperscript{135} Under solvent free conditions, slow addition of 227 to these terminal alkenes (233) in the presence of a catalytic tetrakis(triphenylphosphine)palladium(0) at 65 °C leads to the formation of cyclic ureas 234 in good yield with complete regio- and stereoselectivity (Scheme 98). Furthermore, the catalytic asymmetric version of this allylic/homallylic diamination was readily achieved via the incorporation of a chiral ligand. When subjecting mono- and disubstituted alkenes (235) to a catalytic amount of Pd$_2$(dba)$_3$ with H$_8$-BINOL-derived phosphorus amidite 236 as the chiral reagent, the corresponding cyclic ureas (237) are furnished in high yield and up to 95% ee.\textsuperscript{136}

**Scheme 98.** Symmetric and Asymmetric Pd-Catalyzed Dehydrogenative Allylic/Homallylic Diaminations

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\[
\begin{align*}
\text{Me}_2\text{N}_2\text{Me}_2\text{N} (2.75 \text{ equiv}) + \text{R}_1\text{CH} = \text{R}_2 \xrightarrow{\text{Pd[PPh}_3\text{]_4} (5 \text{ mol\%})} \text{Me}_2\text{N}_2\text{Me}_2\text{N} (2.5 \text{ equiv}) + R_1 & \rightarrow \text{R}_1 = \text{Ph, n-C}_8\text{H}_{13}, \text{CHCH}_2\text{Me}, \text{Obn} \\
\text{Me}_2\text{N}_2\text{Me}_2\text{N} (2.5 \text{ equiv}) + \text{R}_1\text{CH} = \text{R}_2 & \xrightarrow{\text{Pd[dbac]} (5 \text{ mol\%})} \text{Me}_2\text{N}_2\text{Me}_2\text{N} (2.5 \text{ equiv}) + \text{R}_1 \rightarrow \text{R}_1 = \text{Ph, n-C}_8\text{H}_{13}, \text{Bn(Me)}_2\text{N}, \text{R}_2 \rightarrow \text{H, n-Bu}
\end{align*}
\]
```

Another notable discovery made by Shi and colleagues is that the use of copper(I) salts and phosphine ligands can effectively determine the regiochemistry of diamination when using diaziridinone 227 in the presence of conjugated dienes and trienes. One system shows that a combination of copper(I) chloride and triphenyl phosphite (P(OPh)$_3$) readily promotes the diamination reaction of 227 with dienes and trienes (238) exclusively at the terminal position (Scheme 99).\textsuperscript{137} Conversely, when starving the reaction system of phosphine ligands, copper(I)


salts, particularly copper(I) bromide, direct diene diamination to the internal alkene position.\textsuperscript{138} Both respective approaches achieve their corresponding diamination in modest to good yield.

\section*{Scheme 99. Phosphine-Ligand-Dependent Regioselective Diaminations of Conjugated Dienes and Trienes}

\begin{center}
\includegraphics[width=\textwidth]{scheme99.png}
\end{center}

Shi has also applied this copper(I)-phosphine ligand combination to the synthesis of 1,2-diamines from aryl-activated 1,1-disubstituted olefins (242).\textsuperscript{139} When employing catalytic quantities of copper(I) chloride and triphenylphosphine in a 1:1 ratio, a wide range of styrene derivatives (242) can undergo diamination with di-\textit{tert}-butyldiaziridinone at elevated temperatures resulting in the formation of desired imidazolidinones (243) in high yield (Scheme 100). Additionally, naphthyl-derived alkenes are tolerated thereby broadening the substrate scope.

\section*{Scheme 100. Copper(I)-Catalyzed Diamination of Disubstituted Terminal Alkenes}

\begin{center}
\includegraphics[width=\textwidth]{scheme100.png}
\end{center}

As for nitrogen sources, Shi has reported that motifs other than di-\textit{tert}-butyldiaziridinone (227) have proven effective for alkene diamination. \textit{N,N}-di-\textit{tert}-butylthiadiaziridine 1,1-dioxide (244) can undergo addition to a range of activated alkenes to afford cyclic sulfamides.\textsuperscript{140} For example, when styrene (146) is treated with thiadiaziridine dioxide 244 in the presence of a CuCl-P(\textit{n}-Bu)\textsubscript{3} combination, sulfamide 245 is furnished in 94\% isolated yield (Scheme 101). In an analogous manner, di-\textit{tert}-butyldiaziridinimide 246 can be used to promote the diamination of various alkenes en route to their corresponding cyclic \textit{N}-cyano guanidines.\textsuperscript{141} To illustrate, 4-


vinylbiphenyl (247) is readily transformed to cyano guanidine 248 in 86% yield upon exposure to a CuCl-P(PPh₃)₃ system with diaziridinimide 246 as the nitrogen source.

**Scheme 101.** Copper(I)-Catalyzed Alkene Diaminations with Thiadiaziridine Dioxide 244 and Diaziridimine 246

Pericyclic reactions provide a pathway to 1,2-diamines from alkenes. Among the most notable approaches is that reported by Sharpless and Singer in which they use selenium dioxide bis(amide) 249 to accomplish alkene diamination with exclusive cis selectivity.²⁴² Bis(amide) 249 is generated in situ by the oxidation of selenium powder in the presence of p-toluenesulfonamide (250) and its sodium salt (251) (Scheme 102). This compound can then undergo a [4+2] cycloaddition with cyclic 1,3-diene 252 to yield cycloadduct 253. Subsequent ring-opening with p-toluenesulfonamide affords 254, which undergoes a [2,3]-sigmatropic rearrangement to give 255. The desired cis-diamine product (256) is furnished upon desulfurization of selenium(II) amide 255.

**Scheme 102.** 1,2-Diamination of 1,3-Dienes with Selenium Dioxide Bis(Imide) 249

Numerous halogen-mediated approaches have been employed for the synthesis of vicinal diamines from alkenes. One method, in particular, that has proven effective is the use of

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dihaloarylsulfonamide-acetonitrile combinations. This type of reaction system was first reported in 2003 by Li and colleagues in order to promote the imidazolination of α,β-unsaturated carbonyl compounds.\(^\text{143}\) Treatment of α,β-unsaturated ketones and esters, such as methyl cinnamate (257), with \(N,N\)-dichloro-\(p\)-toluenesulfonamide (258), 4 Å molecular sieves, and the complex generated from \(\text{Rh}_2(\text{pbf})_4\) and \(\text{PPh}_3\) in the presence of acetonitrile affords the desired \textit{trans}-substituted 2-dichloromethyl-2-imidazolines 259 in moderate to high yield and with excellent diastereoselection (Scheme 103). This type of transformation is thought to proceed through a Ritter-type reaction of an aziridinium ion intermediate.

**Scheme 103.** Imidazolination of α,β-Unsaturated Ketone 257 with a TsNCl\(_2\)/MeCN/Rh\(_2\)(pbf)\(_4\)•PPh\(_3\) Reagent Combination

Subsequent studies by Li and co-workers have revealed that the same imidazolination of α,β-unsaturated carbonyl compounds can be achieved with a more reactive dihaloarylsulfonamide in the absence of a catalyst.\(^\text{144}\) When enone 260 is treated with \(N,N\)-dichloro-2-nitrobenzenesulfonamide (261), 4 Å molecular sieves and acetonitrile, the corresponding dichloromethyl diamine (262) is furnished in 71% isolated yield and with high levels of diastereoselectivity (Scheme 104). Li further improved on his findings by developing a protocol that avoids the inconvenience of handling unstable \(N,N\)-dichlorosulfonamides 258 and 261.\(^\text{145}\) Exposure of enone 260 to \(p\)-toluenesulfonamide (250) and \(N\)-chlorosuccinimide (NCS) at 50 °C results in the \textit{in situ} generation of dichlorosulfonamide 258, ultimately yielding the expected imidazoline product 262 in sufficient yield and d.r.

**Scheme 104.** Improved Methods for the Direct Imidazolination of α,β-Unsaturated Ketones

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In a related approach, Wang and colleagues reported a system that incorporates NCS, NaN₃, and NaI as the additive, to promote the inter/intramolecular aminoazidation of γ-alkenyl protected amines en route to azidopiperidines. To demonstrate, alkenyl protected amine 263, when subjected to this NCS, NaN₃, and NaI combination at elevated temperatures, readily converts to azidopiperidine 264 in 92% yield (Scheme 105). It should be noted that this inter/intramolecular aminoazidation displays high favorability towards its 6-endo-trig piperidine product relative to its 5-exo-trig pyrrolidine regioisomer.

**Scheme 105. Inter/Intramolecular Aminoazidation of γ-Alkenyl Amines with NCS, NaN₃, and NaI**

Other chloroamine-acetonitrile systems have proven sufficient for the diamination of olefins. In 2003, Booker-Milburn and co-workers reported a one-pot method for cis-imidazolination of alkenes via the use of an N-chlorosaccharin-acetonitrile-KOEt combination (Scheme 106). Styrene (146), when exposed to acetonitrile, can undergo a Ritter-type reaction with the electrophilic chlorinating agent N-chlorosaccharin (265) to arrive at nitrilium ion 266. Subsequent capture of 266 with the saccharin anion affords β-chlorosulfonylamidine 267, which upon treatment with KOEt undergoes an intramolecular cyclization to give imidazoline 269.

**Scheme 106. cis-Imidazolization of Alkenes with N-Chlorosaccharin, CH₃CN, and KOEt**

Ramesh and Kumar have also shown that chloramine-T in acetonitrile can be used to facilitate the diamination of enol ethers.\(^{148}\) To illustrate the efficacy of this one-pot method, treatment of tri-\(\alpha\)-acetyl-\(\alpha\)-glucal (270) with stoichiometric amounts of chloramines-T in the presence of catalytic iodine results in the formation of \(\beta\)-\(\alpha\)-gluco 1,2-disulfonamide 271 in 69% isolated yield (Scheme 107).

**Scheme 107. Diamination of Glucal 270 Using I\(_2\) and Chloroamine-T**

Iodine azide (IN\(_3\)) is another halogen-based reagent that can be used for the diamination, more specifically diazidation, of olefins. Sasaki demonstrates the utility of this substrate through the diazidation of medium-sized cyclic alkenes.\(^{149}\) For example, when subjecting tropone ethyleneketal (272) to both iodine azide and sodium azide in acetonitrile, iodoazide 273 is furnished, although not isolated (Scheme 108). Subsequent displacement of the iodide group with excess azide gives unstable diazide 274, which is trapped as its respective 1,3-dipolar cycloadduct (275) upon treatment with dimethyl acetylenedicarboxylate (DAC).

**Scheme 108. Diazidation of a Cyclic Polyene with IN\(_3\) and NaN\(_3\)**

Tamura has also reported that this iodine azide/sodium azide combination can readily promote the diazidation of benzofurans (Scheme 109).\(^{150}\) The mechanistic pathway, however, is slightly different. Exposure of benzofuran 276 to IN\(_3\) yields iodoazide 277. Elimination of the iodide moiety results in the formation of oxonium 278. A second equivalent of azide can add into the oxonium, affording the desired diazide in 93% yield, but with low levels of diastereoselection.


Furthermore, acyl and tosyl indoles can be converted to their corresponding diazides under the same reaction conditions and through an analogous mechanistic pathway.\(^{151}\)

**Scheme 109.** Diazidation of Benzo-furans and Indoles with IN\(_3\)

To expand on the versatility of iodine azide, this reagent can be used to transform trans-stilbenes to their corresponding 1,2-diaryl-1,2-diazidoethanes (Scheme 110).\(^{152}\) When trans-stilbene 280 is treated with IN\(_3\) in the presence of excess azide, diazidoethane 281 is furnished in 65% yield and with high d.r. The fact that the anti-addition product is acquired in such large excess relative to its syn-adduct indicates that this transformation may go through a β-azidocarbocation intermediate. Trapping of excess azide from the less hindered face would give the anti-product of 281.

**Scheme 110.** Diazidation of trans-Stilbene 280 Using IN\(_3\)

Additionally, 1,3-diene systems can undergo 1,2-diazidation as reported by Hassner.\(^{153}\) In this particular study, the reaction of \(E,E\)-diphenylbutadiene (282) with IN\(_3\) generates diazide 283 in 60% isolated yield. Hassner also showed that the treatment of the same diene (282) with BrN\(_3\) in pentane affords bromoazide analog 284 in 80% yield (Scheme 111).

**Scheme 111.** Hassner’s Divergent Reactions of Diene 282 with BrN\(_3\) and IN\(_3\)

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Another pathway that has proven fruitful for the synthesis of vicinal diamines is the intermolecular aminohalogenation of alkenes. Though the competitive oxidation of alkyl and aryl amines may be problematic, Lavilla and colleagues have reported a highly efficient method for the vicinal diamination of 1,4-dihydropyridines in the presence of iodine (Scheme 112). Exposure of N-alkyl-1,4-dihydropyridine 285 to I\(_2\) and an excess of pyrrolidine leads to the formation of trans-2,3-diaminotetrahydropyridine 286 in high yield. Mechanistically, it is believed that the iodonium intermediate formed from the reaction of the olefin with I\(_2\) is opened with pyrrolidine to arrive at intermediate 287. Internal displacement of the iodide generates an aziridinium ion which then undergoes ring opening at the 1-position with another equivalent of pyrrolidine to give the desired diamine.

![Scheme 112. Iodine-Mediated Vicinal Diamination of 1,4-Dihydropyridine 285](image)

In 2012, Hennecke and co-workers reported the use of NIS to promote the doubly intramolecular diamination of alkenes en route to 2,2'-bipyrrrolidines. When phenyl-derived alkenyl diamine 288 was subjected to a stoichiometric amount of NIS in dichloromethane, bipyrrrolidine 289 was furnished in 67% yield (Scheme 113). A number of other aryl- and alkyl-substituted alkenyl diamines were also tolerated, and anti-selective diamination was consistently observed.

![Scheme 113. Intramolecular anti-Selective Diamination of Alkenes with NIS en Route to 2,2'-Bipyrrrolidines](image)

Halogen-mediated cycloguanidinations of alkenes have been explored to a considerable degree. The first reports of this form of alkene diamination were made by Al-Mourabit and colleagues when they demonstrated the bromine-mediated cycloguanidination of N-acylated

Treatment of carboxemethoxydihydropyridine (290) with bromine or NBS in the presence of excess Boc-guanidine afforded bicycles 291a and 291b. Subsequent acid-mediated deprotection of the Boc groups furnished cyclic guanidine 292 in 71% isolated yield (Scheme 114). Tepe and co-workers utilized a closely related cycloguanidination step in their recent synthesis of oroidin-type alkaloid (±)-dibromophakellin (293). When dipyrrolopyrazinone 294 was exposed to Boc-guanidine in the presence of NBS, cyclic guanidine 295 could be furnished, albeit in 29% yield. Acid-mediated deprotection of the Boc moiety proceeded more smoothly as dibromophakellin was obtained in high yield (Scheme 115).

Further studies by Al-Mourabit revealed that 2-aminopyrimidine (296) can also be used as a guanidinating agent (Scheme 116). Treatment of N-acylpyrrole tetrahydropyridine 297 with NBS in the presence of 2-aminopyrimidine results in the formation of intermediate 298. Subsequent displacement of the bromide group and generation of HBr gives the desired guanidine (299) in 52% isolated yield.

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Recently, Zhang and co-workers reported the use of NIS to promote the doubly intramolecular diamination of \(N\)-alkenyl thioureas\(^{159}\). For example, treatment of benzyl-protected alkenyl thiourea 300 with stoichiometric quantities of NIS in the presence of NaHCO\(_3\) afforded diamination product 301 in 34\% yield (Scheme 117). Additionally, aminosulfuration was observed as a competitive process as aminosulfuration product 302 was isolated in 22\% yield from the same reaction mixture.

**Scheme 117.** Zhang’s NIS-Mediated Doubly Intramolecular Diamination of \(N\)-Alkenyl Thioureas

Hypervalent iodine reagents display high synthetic utility in the field of alkene diamination. In light of their ready availability, low toxicity, and reduced environmental impact, these iodine(III) species have gradually replaced a number of heavy metal-mediated protocols. Among the earliest methods of using aryl-\(\lambda^3\)-iodanes en route to diamination is that reported by Zbiral and Ehrenfreund. Here, unsaturated esters (303) are subjected to the combination of PhI(OAc)\(_2\) and TMSN\(_3\) to achieve the synthesis of vicinal diazides (304). Despite the advance, this approach suffered from low yields and a very limited substrate scope (Scheme 118)\(^{160}\).

**Scheme 118.** Diazidation of \(\alpha,\beta\)-Unsaturated Esters with PhI(OAc)\(_2\)

Moriarty and Khosrowshahi later reported a similar, but considerably more effective iodine(III)-mediated alkene diazidation\(^{161}\). When subjecting alkenes, such as \(\text{trans-}\beta\)-methylstyrene (305) to the combination of sodium azide and iodosobenzene in the presence of acid at elevated temperatures, iodonium ion intermediate 306 is formed (Scheme 119). Subsequent displacement of the iodonium species with azide affords diazide 307 in 69\% yield and in 9:1 d.r. Further success of this reaction was demonstrated as benzofuran and indole scaffolds are readily converted to their respective diazides as well.


Alkene diazidation can also be achieved through the use of iodosobenzene in conjunction with trimethylsilyl azide (TMSN₃). Armimoto and co-workers illustrate the efficacy of this hypervalent iodine/silyl azide combination via the smooth conversion of allylsilanes to their corresponding vicinal diazides (Scheme 120). Additionally, Magnus and colleagues show that this same reagent combination can promote the diazidation of triisopropylsilyl (TIPS) enol ethers under chilled conditions. For example, reaction of enol ether 312 with iodosobenzene and TMSN₃ in the presence of catalytic amounts of TEMPO at -78 °C affords diazide 313 in 91% isolated yield. Yet, if the same reaction is run at 0 °C, β-azidation (314) is observed. Thus, diazidation of enol ethers with iodine(III) and azide is highly dependent on temperature.

**Scheme 119. Synthesis of Vicinal Diazides Using Iodosobenzene**

![Scheme 119](image)

**Scheme 120. Vicinal Diaminations of Alkenes Employing PhIO/TMSN₃**

![Scheme 120](image)

In 2011, Muñiz and co-workers reported a breakthrough method that employs a chiral hypervalent iodine species to promote the doubly intermolecular, enantioselective diamination of styrenes (Scheme 121). Aside from being metal-free and practical, this approach is notable as it is the first example of a doubly intramolecular, enantioselective alkene diamination. When using bis(mesylimide) as the nitrogen source in the presence of Ishihara’s C₂-symmetric

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Chiral iodane 315, a variety of styrenes can be converted to their respective diamines in good yields and with high levels of enantioselection.

Scheme 121. Muñiz’s Enantioselective, Metal-Free Intermolecular Diamination of Styrenes

Furthermore, Muñiz and colleagues were able to apply this methodology towards the synthesis of the immunomodulator and veterinary anthelmintic (S)-levamisole (316) (Scheme 122). Styrene (146) is converted to masked diamine 317 in good yield and ee via the enantioselective diamination as previously described. Hydride reduction of 317 with Red-Al afforded bis-mono protected diamine 318 in 86% isolated yield. Benzoylation, radical desulfination, and acid hydrolysis afforded the corresponding unmasked diamine as the bis-HCl salt (319) in 77% yield over 3 steps. Liberation of 319 to its free base form and subsequent treatment with carbon disulfide results in the formation of the precursor mercaptoimidazoline. This intermediate can then be treated with ethylene dibromide under basic conditions in order to furnish (S)-levamisole (316) (30% yield over 2 steps).

Scheme 122. Muñiz’s Enantioselective Synthesis of (S)-Levamisole via Intermolecular Diamination

Muñiz continued to demonstrate the efficacy of hypervalent iodine in doubly intermolecular vicinal alkene diaminations by considerable scope expansion (Scheme 123). When using bis(tosylimide) as the nitrogen source in the presence of PhI(OAc)₂, a variety of styrenes were readily transformed to their desired diamines in high yields. The bis(mesitylimide) diamine library was also significantly expanded via microwave irradiation. It is also notable that the diamine library was not limited to just styrene substrates. Numerous alkyl-substituted alkenes were

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converted to their respective bistosylimide diamine scaffolds upon exposure to PhI(OAc)₂ as well.¹⁶⁶

**Scheme 123.** Iodine(III)-Promoted Intermolecular Diaminations of Styrenes and Alkyl-Substituted Alkenes

Dinuclear iodine(III) species also proved effective in inter/intermolecular alkene diamination as described by Muñiz and colleagues (Scheme 124).¹⁶⁷ Upon reaction optimization, treatment of styrene (146) with substoichiometric quantities of bisimido dinuclear iodine(III) species 320 and stoichiometric quantities of bis(tosylimide) afforded diamine 321 in 74% isolated yield. Additionally, deoxygenated dinuclear iodine(III) compound 322 showed slightly superior reactivity as styrene was converted to 323 without the need for external bistosylimide.

**Scheme 124.** Intermolecular Alkene Diaminations via the Use of Dinuclear Iodine(III)

To complement iodine(III)-promoted inter/intermolecular alkene diaminations, Chiba and colleagues reported that hypervalent iodine promotes inter/intramolecular vicinal diamination of alkenes (Scheme 125).¹⁶⁸ Here, a variety of amidines are smoothly converted to their desired

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dihydroimidazoles upon exposure to PhI(NTs$_2$)$_2$ or PhI(NMs$_2$)$_2$. For example, when amidine 324 is subjected to PhI(NTs$_2$)$_2$ in dichloromethane at elevated temperatures, dihydroimidazole 325 is provided in 79% yield. The bismesylimide analog (326) can also be furnished when PhI(NMs$_2$)$_2$ is employed as the source of iodine(III).

**Scheme 125.** Inter/Intramolecular Alkene Diamination with PhI(NTs$_2$)$_2$ and PhI(NMs$_2$)$_2$

![Scheme Image]

In 2014, Hong and Johnston demonstrated a highly efficacious inter/intramolecular alkene diamination approach that utilizes PhI(OAc)$_2$ and KI en route to forming 3-aminoindolines (Scheme 126).$^{169}$ Here, tosyl-protected vinylaniline 327 can be treated with an array of commercially available primary and secondary amines in the presence of the aforementioned oxidant/additive combination in order to provide desired indoline compounds (328) in moderate to high yields.

**Scheme 126.** Inter/Intramolecular Diaminations of Vinylanilines en Route to 3-Aminoindolines

![Scheme Image]

As for iodine(III)-mediated doubly intramolecular vicinal dianimations of alkenes, notable discoveries have been made by both Muñiz and Shi. Muñiz and co-workers reported that a

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halide/oxidant (KBr/PhI(OAc)\textsubscript{2}) combination, similar to that of Hong and Johnston’s work, can promote the diamination of alkenyl sulfamides (329) to their corresponding cyclic sulfamides (330) in practically quantitative yields (Scheme 127).\textsuperscript{170} Shi and colleagues reported that a variety of formamidines (331) can be converted to their respective tricyclic ureas (332) upon treatment with NIS and PhI(OAc)\textsubscript{2} under very mild conditions (Scheme 128).\textsuperscript{171}

**Scheme 128.** PhI(OAc)\textsubscript{2}/NIS-Mediated Intramolecular Diamination of Formamidines

Wirth and co-workers further pioneer intra/intramolecular vicinal diaminations by reporting an enantioselective version of this type of diamination using chiral hypervalent iodine catalyst 333 (Scheme 129).\textsuperscript{172} Through reaction optimization, it was found that iodine(III) species 333 in the presence of TMSOTf and BF\textsubscript{3}•OEt\textsubscript{2} could readily convert diaminosulfone 334 to cyclic diaminosulfone 335 in good yield and with excellent enantioselection. This highly enantioselective approach was applied to the formation of numerous diamino heterocyclic products as shown in Scheme 129.

**Scheme 129.** Wirth’s Enantioselective Intramolecular Diaminations en Route to Diamino Bicycles

5.3. Reaction Optimization and Substrate Scope

As previously mentioned, Hong and Johnston recently reported a highly efficacious iodine(III)-mediated inter/intramolecular oxidative diamination of terminal alkenes.\textsuperscript{169} By employing a PhI(OAc)\textsubscript{2}/KI oxidant/additive combination in the presence of electron-rich amines,

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tosylated ortho-vinyl aniline 327 was readily converted to a number of 3-aminoindolines (328) under mild and metal-free conditions (Scheme 130). Monosubstituted alkyl and aryl amines as well as disubstituted amines were tolerated, ultimately furnishing a library of over 20 aminoindolines. This metal-free approach is unique as it promotes alkene diamination using a combination of electron-rich and electron-deficient (aryl sulfonamide) nitrogen sources without the need for amine preactivation or protection.

Scheme 130. Hong and Johnston’s Iodine(III)-Mediated Inter/Intramolecular Diamination of Terminal Alkenes

Inspired by the success of this system, we sought to expand this methodology to vinyl phenol motifs with ambitions of directly accessing 3-aminodihydrobenzofurans via an inter/intramolecular aminohydroxylation reaction. Upon subjecting 2-vinyl phenol (336) to stoichiometric quantities of PhI(OAc)$_2$ and KI in the presence of excess thiomorpholine and CH$_3$CN, we found that the desired 3-aminodihydrobenzofuran (337) was not observed (Scheme 131). Instead, diamine 338a was acquired in 48% isolated yield under these reaction conditions (Table 13, entry 1). This result garnered immediate interest as the observed diamine can only be afforded via an unexpected doubly intermolecular alkene diamination pathway.

Scheme 131. Initial Findings of an Iodine(III)-Mediated Doubly Intermolecular Alkene Diamination

With this result in hand, optimization studies of this diamination reaction ensued. Previous mechanistic hypotheses indicate that interaction between PhI(OAc)$_2$ and KI results in the formation of an electrophilic iodinating reagent, which in turn can react with nucleophilic amine to generate an electrophilic $N$-iodamine species.$^{169}$ As an alternative to the PhI(OAc)$_2$/KI combination, NIS could be used as the electrophilic iodinating reagent to provide the iodamine
species required for reactivity. When NIS was employed as the iodinating agent in the presence of 2-vinyl phenol and thiomorpholine, diamine 338a was furnished in 40% yield indicating a slightly inferior reactivity profile compared to the oxidant/additive combination (Table 13, entry 2). Different halide sources in combination with PhI(OAc)\(_2\) were examined next. Use of stoichiometric potassium bromide and ammonium iodide provided diamine 338a in 36% and 40% yields, respectively (Table 13, entries 3 and 4). The combination of oxidant and additive proved essential as starving the reaction conditions of KI or PhI(OAc)\(_2\) resulted in little or no reactivity (Table 13, entries 5 and 6). Upon increasing the amount of amine to 3 equivalents, full conversion of starting material was observed leading to a 78% isolated yield of 338a after chromatographic separation (Table 13, entry 7). Interestingly, when 4 equivalents of thiomorpholine were used, inhibition of product formation was observed as 338a was provided in only 57% yield (Table 13, entry 8). The use of another hypervalent iodine reagent, iodosobenzene, in combination with KI, afforded diamine 338a, but in depressed yield relative to PhI(OAc)\(_2\) and KI (Table 13, entry 9).

**Table 13. Initial Optimization Studies of the Doubly Intermolecular Alkene Diamination**

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>additive</th>
<th>amine equiv.</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhI(OAc)(_2)</td>
<td>KI</td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>--</td>
<td>NIS</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>PhI(OAc)(_2)</td>
<td>KBr</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>PhI(OAc)(_2)</td>
<td>NH(_4)I</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>PhI(OAc)(_2)</td>
<td>--</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>--</td>
<td>KI</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>PhI(OAc)(_2)</td>
<td>KI</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>PhI(OAc)(_2)</td>
<td>KI</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>PhIO</td>
<td>KI</td>
<td>3</td>
<td>36</td>
</tr>
</tbody>
</table>

With sufficient reactivity achieved, a variety of solvents were evaluated to see if yield could be further improved. Dichloromethane mitigated product acquisition as 338a was provided in 21% yield (Table 14, entry 2). Product formation was further inhibited when toluene was employed as the solvent (Table 14, entry 3). Ethereal solvents such as THF and 1,4-dioxane proved inferior as the desired diamine was afforded in 6% and 17% yields, respectively (Table 14, entries 4 and 5).
Therefore, it is evident that CH$_3$CN is necessary in order to achieve maximum conversion to product.

Table 14. Solvent Screen of the Doubly Intermolecular Alkene Diamination

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$CN</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>1,4-dioxane</td>
<td>17</td>
</tr>
</tbody>
</table>

In regards to the most optimal reaction conditions up to this point (Table 13, entry 7), one observation of interest for this particular experiment was the cleanliness of the crude NMR data. First off, there was no sign of starting material (2-vinyl phenol) indicating that this reaction proceeded to full conversion. The only compounds that could be observed by NMR of the crude reaction mixture were iodobenzene (as a result of reaction and subsequent decomposition of PhI(OAc)$_2$) and the desired diamine. Additionally, there were no discernible side products. Therefore, quantitative or near-quantitative yield of diamine 338a for this run was expected. Yet after column chromatography, a 78% isolated yield of 338a indicated that there was indeed room for improved yield. Based on the cleanliness of the reaction and the non-quantitative yield acquired, it was hypothesized that the diamine product may decompose to a degree in situ, ultimately owing to a 78% isolated yield rather than a more fruitful and expected yield (>95%). To probe this hypothesis, diamine 338a was subjected to the optimized reaction conditions, but with no amine, to obtain evidence for product decomposition (Scheme 132). Decomposition was observed as only trace quantities of the submitted diamine were isolated upon chromatographic separation.

Scheme 132. Decomposition Experiment with Diamine 338a
This evidence for decomposition provided a basis for yield optimization. When the temperature was lowered to 0 °C, complete and clean conversion of starting material to product was seen, analogous to that of the run at 25 °C. However, upon chromatographic separation, we were delighted to see that diamine 338a was acquired in 99% isolated yield (Table 15, entry 2). Further chilling the reaction to -20 °C mitigated product formation as diamine 338a was afforded in 59% yield after column chromatography (Table 15, entry 3). 0 °C was used as the optimal temperature as desired diamine can be produced while minimizing decomposition or undesired side reactivity.

**Table 15. Effects of Temperature on the Doubly Intermolecular Alkene Diamination**

<table>
<thead>
<tr>
<th>entry</th>
<th>T (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>-20</td>
<td>59</td>
</tr>
</tbody>
</table>

Before developing an amine scope, two things needed to be confirmed: 1) that the PhI(OAc)$_2$/KI combination exhibits superior reactivity relative to NIS, and 2) that the hydroxyl motif of 2-vinyl phenol is essential for reactivity. This involved examining a multitude of alkenes with both sets of reaction conditions. As shown in Table 16, treatment of ortho-hydroxystyrene (2-vinyl phenol) with thiomorpholine (3 equivalents) at room temperature and 0 °C led to diamine 338a in 78% and 99% yields respectively (entries 1 and 2). When NIS was employed as the

**Table 16. Diamination of 2-Vinyl Phenol with PhI(OAc)$_2$/KI and NIS**

<table>
<thead>
<tr>
<th>entry</th>
<th>Method</th>
<th>T (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>0</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>25</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>0</td>
<td>91</td>
</tr>
</tbody>
</table>
electrophilic iodinating reagent at room temperature, the desired diamine was afforded but in slightly lower yield relative to the PhI(OAc)$_2$/KI run (Table 16, entry 3). When the reaction temperature was lowered to 0 °C, NIS once again engaged in diamination, furnishing diamine 338a in 91% isolated yield (Table 16, entry 4). The results acquired with NIS were analogous to those of PhI(OAc)$_2$/KI in the sense that higher yields were acquired when reaction temperature was lowered. Yet, when directly comparing reaction efficacy between PhI(OAc)$_2$/KI and NIS, it was evident that the iodine(III)/additive combination consistently proves superior yield.

The next alkene that was examined was *para*-hydroxystyrene (4-vinyl phenol). This particular alkene was of interest as the lone pairs of the hydroxyl group should still be in conjugation with the terminal alkene. In other words, because the hydroxyl motifs of both 2-vinyl phenol and 4-vinyl phenol are in conjugation with the terminal olefin, nucleophilicity of 2-vinyl phenol and 4-vinyl phenol should be similar. Consequently, diamination with 4-vinyl phenol (339) should be observed. When 4-vinyl phenol was treated with PhI(OAc)$_2$ and KI in the presence of thiomorpholine at room temperature, we were delighted to see that diamine 340a was provided in 51% yield, upon chromatographic separation (Table 17, entry 1). Parallel to the 2-vinyl phenol system, lowering the reaction temperature resulted in increased yield of the desired diamine (62% yield) (Table 17, entry 2). NIS also engaged in diamination at both room temperature and 0 °C, furnishing diamine 340a in 40% and 50% yields, respectively (Table 17, entries 3 and 4). These results once again indicate that better yields are obtained at lower temperature and that the PhI(OAc)$_2$/KI oxidant/additive combination is the superior set of reaction conditions.

**Table 17. Diamination of 4-Vinyl Phenol with PhI(OAc)$_2$/KI and NIS**

<table>
<thead>
<tr>
<th>entry</th>
<th>Method</th>
<th>T (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>25</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>0</td>
<td>50</td>
</tr>
</tbody>
</table>

3-Vinyl phenol (*meta*-hydroxystyrene) was examined next. Unlike *ortho*-hydroxystyrene and *arap*-hydroxystyrene, the lone pairs of the hydroxyl group of *meta*-hydroxystyrene should not
be in conjugation with the terminal alkene. As a result, 3-vinyl phenol (341) should have a decreased nucleophilicity compared to its 2-vinyl phenol and 4-vinyl phenol counterparts. When treating 3-vinyl phenol with the PhI(OAc)₂/KI combination in the presence of thiomorpholine at room temperature, no conversion of starting material could be seen after an 18 hour reaction period (Scheme 133). The same result was observed even after elevation of reaction temperature. Additionally, NIS proved fruitless as only starting material was observed after prolonged reaction times at both room temperature and 65 °C. These results clearly indicate that having the hydroxyl motif ortho or para to the terminal alkene is vital for sufficient reactivity.

**Scheme 133.** Unsuccessful Diamination of 3-Vinyl Phenol with PhI(OAc)₂/KI and NIS

![Scheme 133](image)

To further probe the necessity of a hydroxyl unit at the ortho and/or para positions of styrene, 2-vinylanisole (343) was submitted to the diamination protocol. This substrate was of interest as it possesses an electron-donating motif ortho to the alkene functionality, similar to that of 2-vinyl phenol. Furthermore, the lone pairs of the methoxy motif should be in conjugation with the terminal olefin, giving it a reactivity profile comparable to its ortho-hydroxystyrene analog. However, when 2-vinylanisole was treated with PhI(OAc)₂/KI or NIS in the presence of thiomorpholine, reactivity was mitigated as no corresponding diamine (344) was observed, even with the application of higher temperature (Scheme 134). Based on these findings, it is evident that having a free hydroxyl group as the electron-donating species is critical for the nucleophilicity of the alkene.

**Scheme 134.** Unsuccessful Diamination of 2-Vinylanisole with PhI(OAc)₂/KI and NIS

![Scheme 134](image)
Styrene (146) was the next alkene to be evaluated. With decreased nucleophilicity relative to ortho-hydroxystyrene and para-hydroxystyrene, the expectations for diamination with styrene as the substrate were relatively low. When subjected to the diamination protocol with PhI(OAc)_2 and KI, styrene appeared to be unreactive as predicted (Scheme 135). The same results were observed when NIS was used as the iodinating agent.

**Scheme 135. Unsuccessful Diamination of Styrene with PhI(OAc)_2/KI and NIS**

The next alkene that was employed was allylbenzene (346). With the terminal alkene out of conjugation with the aromatic ring, it was expected that this substrate would be unreactive. Consequently, no diamination (347) was observed when allylbenzene was subjected to either diamination method at ambient or elevated temperatures (Scheme 136).

**Scheme 136. Unsuccessful Diamination of Allylbenzene with PhI(OAc)_2/KI and NIS**

*ortho*-Nitrostyrene (348) was also examined as this was an alkene that benefits from conjugation while being resistant to direct oxidation by PhI(OAc)_2. This, too, failed to convert to

**Scheme 137. Unsuccessful Diamination of *ortho*-Nitrostyrene with PhI(OAc)_2/KI and NIS**
its corresponding diamine (349) when treated with either the oxidant/additive combination or NIS (Scheme 137). Additionally, higher temperatures were implemented, but to no avail.

Given that 2-vinyl phenol and 4-vinyl phenol successfully engaged in diamination, whereas 3-vinyl phenol, 2-vinylanisole, styrene, allylbenzene, and ortho-nitrostyrene proved fruitless, it is evident that the hydroxyl motif of 2-vinyl phenol and/or 4-vinyl phenol is essential for the promotion of reactivity. Furthermore, the diamination protocol employing the PhI(OAc)2/KI combination consistently gave higher yields, in successful cases, compared to the NIS variation. With these findings in hand, one final parameter was to be examined before developing the amine scope: the necessity of a terminal alkene.

All alkenes subjected to diamination up to this point have been terminal alkenes. Given previous findings, we were interested in seeing if internal alkenes could readily undergo diamination. ortho-Styryl phenol (350) was the reagent of choice as it was a 2-vinyl phenol analog that possessed an internal alkene. When ortho-styryl phenol was treated with PhI(OAc)2 and KI in the presence of thiomorpholine, no diamination (351) was observed, resulting in a 45% recovery of starting material (Scheme 138). NIS also proved ineffective, once again resulting in the reacquisition of o-styrylphenol (67% recovery).

Subsequent studies specifically applied the protocol using PhI(OAc)2/KI and the most reactive styrene (ortho-hydroxystyrene) to explore the amine scope of the intermolecular diamination. Beginning with disubstituted amines, diamination with morpholine led to 338b in 79% yield (Table 18, entry 2). Piperidine and isoindoline, a pyrrolidine derivative, led to vicinal diamines 338c and 338d, but with depressed yield (Table 18, entries 3 and 4). Cbz-, Boc-, and ethyl carboxylate-protected piperazines successfully engaged in diamination providing 338e-338g in moderate (59%) to good (90%) yield (Table 18, entries 5-7). These three diamines are notable as they allow for subsequent unmasking of the piperazine moieties under neutral, acidic, or basic conditions.
conditions. N-Arylpiperazines, however, proved less reactive under the diamination protocol as 1-phenylpiperazine and 1-(3-methoxyphenyl)piperazine furnished 338h and 338i in 31% and 16% yields, respectively (Table 18, entries 8 and 9). N-Cinnamylpiperazine displayed high reactivity as vicinal diamine 338j was acquired in 94% isolated yield upon chromatographic separation (Table 18, entry 10). Acyclic disubstituted amines engaged in diamination as dibenzylamine and N-methylbenzylamine led to 338k and 338l in 35% and 65% yields, respectively (Table 18, entries 11 and 12).

**Table 18. Doubly Intermolecular Alkene Diamination: Secondary Amine Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>338</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>C4H8S (thiomorpholine)</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>C4H8O (morpholine)</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>C5H10 (piperidine)</td>
<td>29</td>
</tr>
<tr>
<td>4+</td>
<td>d</td>
<td>C3H6 (isoindoline)</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>R' = Cbz</td>
<td>62</td>
</tr>
<tr>
<td>6+</td>
<td>f</td>
<td>R' = Boc</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>R' = CO2Et</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>R' = Ph</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>R' = MeOCH2Ph</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>R' = CH2CHCH2CH2Ph</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>k</td>
<td>C14H14 (dibenzylamine)</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>l</td>
<td>Me, Bn (N-methylbenzylamine)</td>
<td>65</td>
</tr>
</tbody>
</table>

*3.0 equiv of Ph(OAc)2 used. †2.1 equiv of amine used.

Primary amines were examined next. Subjection of aniline to the diamination protocol at 0 °C led to diamine 338m in 48% yield (Table 19, entry 1). Interestingly, when the same reaction was repeated at room temperature, an improvement of reactivity was observed (Table 19, entry 2). The same phenomenon proved consistent with 4-tert-butylaniline and 3,5-dimethylaniline as diamines 338n and 338o were acquired in significantly higher yields at room temperature relative to 0 °C (Table 19, entries 3-6). One exception to this trend, however, was 4-fluoroaniline as vicinal diamine 338p was isolated in identical yield (47%) at both room temperature at 0 °C (Table 19, entries 7 and 8). Seeing that a number of anilines displayed higher reactivity at room temperature was interesting, since this was opposite the trend observed with disubstituted amines. One hypothesis for explaining these higher yields at room temperature may be the fact that
corresponding aniline diamines (338m-338p) are less prone to decomposition compared to their secondary amine counterparts.

**Table 19. Doubly Intermolecular Alkene Diamination: Primary Amine Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>338</th>
<th>R</th>
<th>T (°C)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>Ph</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>Ph</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>n</td>
<td>4-tBu-C6H4</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>n</td>
<td>4-tBu-C6H4</td>
<td>25</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>o</td>
<td>3,5-dimethyl-C6H3</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>o</td>
<td>3,5-dimethyl-C6H3</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>p</td>
<td>4-F-C6H4</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>p</td>
<td>4-F-C6H4</td>
<td>25</td>
<td>47</td>
</tr>
</tbody>
</table>

For reasons not clear, one class of amines that proved troublesome in this diamination protocol was primary aliphatic amines. Subjection of these amines to the Phl(OAc)2/KI combination in the presence of 2-vinyl phenol gave no sign of desired diamination. A common feature among a number of examples, however, was intermolecular aminoacetoxylation (Scheme 139). For example, when isopropylamine, cyclohexylamine, and 3-methoxypropylamine were subjected to standard reaction conditions, aminoacetoxylation products 352-354 were the only products that were cleanly isolated post-column chromatography.

**Scheme 139. Intermolecular Aminoacetoxylation with Primary Aliphatic Amines**

para-Hydroxystyrene was also an effective precursor for intermolecular vicinal diamination. Although this was previously exemplified with thiomorpholine, successful diamination with morpholine and aniline (340b and 340c) further illustrate that 4-vinyl phenol can
tolerate a number of amine substrates (Table 20, entries 2 and 3). Once again, higher yield was achieved at room temperature for the aniline case.

**Table 20. Doubly Intermolecular Alkene Diamination: Amine Scope with para-Hydroxystyrene**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C_4H_8S (thiomorpholine)</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>C_4H_8O (morpholine)</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>85</td>
</tr>
</tbody>
</table>

*Reaction run at 25 °C.*

Modifications to the vinylphenol precursor were explored, specifically with thiomorpholine, illustrating further generality. Halogen substituents at the 4-position were tolerated as diamination products 338q-338s were furnished in moderate to good yield (Table 21, entries 2-4). Substrates with electron-withdrawing or electron-donating groups at the 4-position also engaged in diamination as 338t and 338u were provided in 50% and 54% yields, respectively (Table 21, entries 5 and 6). Diamination with a hydroquinone species was possible as 338v was afforded, albeit in low yield (Table 21, entry 7). Lastly, vinylphenol substrates possessing electron-rich methoxy groups at the 5- and 6-positions delivered their diamination products (338w and 338x) in moderate (57%) to good yield (83%) (Table 21, entries 8 and 9).

**Table 21. Doubly Intermolecular Alkene Diamination: Vinylphenol Scope**

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>q</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>r</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>s</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>t</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>u</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>v</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>w</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>x</td>
<td>83</td>
</tr>
</tbody>
</table>

*Indicates 3 equivalents of Ph(OAc)_2 (PIDA) used.*
5.4. Control Experiments and Mechanistic Hypothesis

Throughout the course of these exploratory studies for the doubly intermolecular alkene diamination, a number of experiments were directed at the isolation of key intermediates or products along the preferred or competing reaction pathways. Chief among these co-products is bis(oxygenation) product \(355\). This particular product arose from a control experiment in which 2-vinyl phenol was treated with PhI(OAc)\(_2\) and KI alone (no amine). \(^1\)H NMR analysis of the crude reaction mixture showed 3-acetoxydihydrobenzofuran (355) as the major product, and subsequent chromatographic separation provided compound \(355\) in 69% isolated yield (Scheme 140).

Scheme 140. Generation of Bis(oxygenation) Product \(355\)

![Scheme 140](image_url)

Another key product isolated was that of iodoacetoxylation product \(356\). Based on our previous success of alkene diamination with electron-rich amines, we wanted to see if electron-withdrawing amines could also be tolerated. When combining 2-vinyl phenol with the PhI(OAc)\(_2\)/KI combination in the presence of electron-deficient bistosylimide (Ts\(_2\)NH), iodide \(356\) was furnished, albeit in low yield (12%) (Scheme 141).

Scheme 141. Generation of Iodoacetoxylation Product \(356\)

![Scheme 141](image_url)

Isolation of bis(oxygenation) and iodoacetoxylation products \(355\) and \(356\) enabled further studies that could determine if these compounds indeed serve as intermediates en route to diamination. When \(355\) and \(356\) were individually subjected to the standard diamination protocol (PhI(OAc)\(_2\), KI, thiomorpholine, and CH\(_3\)CN) at room temperature, no sign of diamine \(338\) could be detected (Scheme 142). Furthermore, neither of those intermediates is observed directly during the conversion of 2-vinyl phenol (336) to diamination product \(338\) under the same reaction conditions. What has been determined, however, is iodide \(356\) and 3-acetoxydihydrobenzofuran (355) are united in a common pathway. This was confirmed as phenol 356 converts to 355 when exposed to PhI(OAc)\(_2\)/KI in the absence of amine or when treated with amine alone.
These intermediates were of interest as they provide useful mechanistic insight. These products appear to collectively arise from electrophile addition to the terminal carbon, followed by nucleophilic addition to the benzylic carbon. It is speculated that carbon-nitrogen bond formation via an electrophilic amine formed in situ is a key aspect of the actual mechanism leading to diamination. Additionally, this speculation of electrophilic amine addition (terminal carbon) and subsequent nucleophilic addition (benzylic position) is reflective of the aminoacetoxylation products depicted in Scheme 139. Non-nucleophilic amines such as Ts₂NH did not provide diamination product, even when applying the protocol developed by Muñiz (Scheme 143). Instead, monoamination product 357 was afforded in low yield, perhaps through a pathway analogous to 336 → 356 → 355. This result is also consistent with the unique reactivity of an electrophilic amine using the Phl(OAc)₂/KI protocol.

A plausible reaction mechanism is depicted in Figure 24. When KI interacts with Phl(OAc)₂, it is believed that the iodide substitutes for one of the acetoxy groups, generating electrophilic iodinating agent A. This particular iodane (A) can activate the amine (B) through iodamine formation (C). The success of NIS in this transformation further suggests that the formation of an iodamine is key in the reaction pathway. Subsequent attack of the halamine by the
alkene moiety of 2-vinylphenol generates intermediate D. The lone pairs of electrons on the hydroxyl unit can resonate in order to break open the aziridinium, resulting in ortho-quinone methide E. This intermediate serves as a suitable electrophile for nucleophilic attack of amine en route to homodiamination (F).

**Figure 24. Mechanistic Hypothesis for Phl(OAc)₂/KI-Mediated Intermolecular Diamination**

One of the key features in regard to the mechanistic pathway described above is the regeneration of iodide. Because it is hypothesized that iodide is regenerated *in situ*, it is plausible that diamination can be achieved when employing substoichiometric or catalytic quantities of halide. While previous studies employed a full equivalent of KI in order to apply general conditions

**Table 22. KI Loading Study**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst loading</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 mol%</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>1 mol%</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>2 mol%</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>3 mol%</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>4 mol%</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>5 mol%</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>10 mol%</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>30 mol%</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>50 mol%</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>100 mol%</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>120 mol%</td>
<td>96</td>
</tr>
</tbody>
</table>
to a broad collection of substrates, a series of experiments were designed to vary KI loading in the
diamination of 2-vinyl phenol (336) with thiomorpholine.

Starving the reaction conditions of the additive resulted in minimal background reactivity
(6% yield) (Table 22, entry 1). Yet, when a 1 mol% loading of KI was used, reactivity increased
nearly six-fold as diamination product 338a was isolated in 34% yield (Table 22, entry 2). Progressively increasing the iodide loading led to higher yield (Table 22, entries 3-6). This was
reflected through a 10 mol% loading, which correlated to a 74% yield of 338a (Table 22, entry 7).
Despite observing sufficient reactivity with catalytic halide loadings, further studies confirmed
that substoichiometric and even stoichiometric amounts of KI (Table 22, entries 8-11) were
necessary in order to achieve optimal yield (Figure 25).

![Figure 25. Relative Comparison of KI Loading and Reactivity](image)

5.5. Future Work

Although this doubly intermolecular diamination with 2-vinylphenol was met with a high
degree of success, other avenues can be explored in order to make this system even more efficient.
One particular direction to pursue is heterodiamination of 2-vinylphenol. As described previously,
this diamination protocol was tolerant to a wide array of amines. One of the main drawbacks,
however, is that the amine moieties are identical at both sites of diamination (i.e.
homodiamination). If two different amines, such as aniline and thiomorpholine, can be
regioselectively installed at these positions through reaction optimization, a much higher level of
generality would be achieved for this reaction system (Scheme 144).
The enantioselective variation of this system is another route to be taken. This can be probed by subjecting a number of chiral organocatalysts (e.g. PBAM) to the previously developed protocol (Scheme 145). Another plausible approach towards achieving enantioselection would be the use of a chiral hypervalent iodine reagent as employed by Muñiz and Ishihara.\textsuperscript{164,165} If this strategy proves fruitless, \textit{in situ} generation of chiral iodine(III) via incorporation of chiral iodoarenes and MCPBA would be another possibility. These investigations are currently ongoing within our laboratory.

\textbf{Scheme 145. Potential Enantioselective Variations of the Doubly Intermolecular Alkene Diamination}
Chapter 6. A Unified Approach to the Four Azaindoline Families by Inter-/Intramolecular Annulative Diamination of Vinylpyridines

6.1. Background

The indoline scaffold is considered to be one of the most privileged structures in nature.\textsuperscript{173} It is found in a variety of naturally bioactive alkaloids and is the structural component of several pharmaceutically active compounds. Because of their strong biological profile, indolines have garnered a high degree of interest and have been synthesized via a number of methodologies as a result.\textsuperscript{174}

\textbf{Figure 26.} Examples of Naturally Bioactive Alkaloids Possessing an Indoline Scaffold

Vinblastine (358) is among the bioactive alkaloids that possess an indoline core (Figure 26). This natural product is of considerable importance as it has been used to treat numerous types of cancer such as Hodgkin’s lymphoma,\textsuperscript{175} non-small cell lung cancer,\textsuperscript{176} bladder cancer,\textsuperscript{177} brain cancer,\textsuperscript{178} and testicular cancer.\textsuperscript{179} Other indoline-containing alkaloids with biological significance

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{174} For a review of methods that access the indoline scaffold, see Liu, D.; Zhao, G.; Xiang, L. \textit{Eur. J. Org. Chem.} \textbf{2010}, 3975-3984.
\item \textsuperscript{179} Hanna, N.; Einhorn, L. \textit{J. Clin. Oncol.} \textbf{2014}, 32, 3085-3092.
\end{itemize}
\end{footnotesize}
include ajmaline (359), an antiarrhythmic agent,\textsuperscript{180} (−)-physostigmine (360), a cholinesterase inhibitor,\textsuperscript{181} and (+)-aspidospermidine (361), which shows strong antimalarial activity.\textsuperscript{182} Although strychnine (362) is classified as an alkaloid that bears an indoline moiety, this particular natural product suffers from a high toxicity profile and is therefore used as a common pesticide.\textsuperscript{183}

One of the most notable pharmaceutical agents with an indoline backbone is pentopril (363). Previous studies confirm that pentopril displays angiotensin-converting enzyme (ACE) inhibition and is therefore considered an antihypertensive drug (Figure 27).\textsuperscript{184} Silodosin (364) is another pharmaceutical that possesses an indoline framework. This compound is an \(\alpha_{1a}\)-adrenoceptor (AR) antagonist and is used as medication for the treatment of problems associated with the human prostate.\textsuperscript{185} Other indoline-bearing pharmaceutical candidates include small-molecule MDM2 inhibitor MI-219 (365), a promising anticancer agent,\textsuperscript{186} as well as 3-aryl-N-acylindoline 366, which has been recently reported to target inhibitors of apoptosis proteins (IAP).\textsuperscript{187} These listed examples constitute only a small portion of the biological impact that these compounds have as SciFinder identifies more than 1300 references where indolines have been described as antibacterials, kinase inhibitors for cancer targets, antidiabetic agents, anti-inflammatory agents, and analgesics.\textsuperscript{188}

**Figure 27. Examples of Pharmaceutical Agents Possessing an Indoline Scaffold**

![Examples of Pharmaceutical Agents Possessing an Indoline Scaffold](image)

Despite its prominence in natural products and pharmaceutical agents, one of the main limitations of the indoline scaffold from a pharmacological standpoint is that it possesses a
constrained aniline motif. The aniline moiety is a well-known structural alert, a chemical fragment that is associated with adverse in vivo outcomes and/or adverse drug reactions (ADRs). These outcomes include but are not limited to mutagenicity, direct toxicity, carcinogenicity, DNA intercalation, or idiosyncratic toxicity. ADRs (and subsequent toxicity) from anilines are caused by two types of bioactivations: 1) hydroxylation of the aromatic ring resulting in reactive iminoquinones (367) and 2) oxidation of the amine which leads to reactive nitrenium (368) or nitroso (369) derivatives (Scheme 146).

One of the most direct ways to de-risk the aniline structural alert is to incorporate one or more nitrogens into the phenyl ring. These nitrogens will reduce the electron density of the aromatic ring, rendering oxidation to species 367-369 more difficult. Thus, the development of azaindoline pharmaceuticals is seen as novel approach to improve pharmacological profiles. Devillers and colleagues demonstrate this in their respective synthesis of a potent phosphodiesterase-4 (PED4) inhibitor. They report that high throughput screening and initial structure activity relationship (SAR) studies led to the identification of 9-amino-tetrahydrodiazepinoindole compound CI-1044 (370). Despite showing high potency for PED4 inhibition, the aniline structural fragment within CI-1044 (370) was considered to be a toxicophore. To address for this unwanted toxicity, the aniline moiety was replaced with an azaindoline residue via the synthesis of triaza-benzoazulen-9-one 371 (Figure 28). Other substituents such as a methoxy group at the 9-position and a nicotinic acyl side chain were chosen based on further SAR evaluation. When tested for PDE4 inhibition, compound 371 showed

\[ \text{Scheme 146. Aniline Bioactivation Pathways} \]

comparable potency relative to 370 indicating that the activity range was conserved with the replacement of the aniline moiety. The difference, however, is that benzoazulenone 371 has a better pharmacological profile since the azaindoline scaffold derisks the aniline structural alert contained within the indoline analog (370).

**Figure 28.** Phosphodiesterase Inhibition of Aniline and Azaindoline Compounds 370 and 371

Sumiyoshi and co-workers utilized a similar approach in their search for selective M₁ and M₄ muscarinic acetylcholine receptor (mAChRs) agonists.²⁹¹ High throughput screening led to the identification of indoline spiropiperidine 372 as a hit compound (Figure 29). To account for potential ADRs from the aniline motif within compound 372, azaindoline analog 373 was synthesized as an initial lead compound. Further SAR studies led to the identification of compound 374, which showed selective M₁ and M₄ mAChRs agonist activity and has good potential as an orally available antipsychotic with a novel mechanism of action.

**Figure 29.** mAChR Agonist Activity of 7-Azaindoline Compounds 373 and 374

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Based on these examples, it is evident that the azaindoline scaffold serves as a nice surrogate for the aniline moiety. Because of their reduced risk of ADRs and minimal effect on promising biological activity, acquisition of azaindoline-containing pharmaceutical candidates is of high importance. The most efficient means of accelerating the syntheses of these types of compounds is through developing new methodologies that readily access azaindoline functionalities.

6.2. Known Methods for the Preparation of Azaindolines

The azaindoline motif has been successfully synthesized via a variety of protocols. Although numerous methods have been employed in order to arrive at each azaindoline ring system, there is only one unified approach that readily accesses all four isomeric azaindolines. Of these four isomeric families, the most accessible azaindoline backbone to date is the 7-azaindoline core.

Among the earliest reports of successfully synthesizing the 7-azaindoline framework is that of van der Plas and colleagues. Here, they utilize an intramolecular inverse electron demand Diels-Alder reaction of pyrimidines with side chain dienophiles in order to furnish the desired bicyclic system. When pyrimidine 375 is subjected to high temperature, the intramolecular [4+2] cycloaddition provides intermediate 376 (Scheme 147). This intermediate is then converted to acetylated 7-azaindoline 377 in situ upon the release of hydrogen cyanide (HCN).

Scheme 147. Synthesis of 7-Azaindolines via an Inverse Electron Demand Diels-Alder Reaction of Pyrimidines

In a closely related manner, Taylor and co-workers report the use of an intramolecular inverse electron demand Diels-Alder reaction of 1,2,4-triazines bearing side chain dienophiles to promote the formation of 7-azaindoline motifs. Exposure of these triazine compounds (378) to elevated temperatures facilitates the cycloaddition generating the corresponding tricyclic

intermediates (379) \textit{in situ} (Scheme 148). Conversion of these cycloadducts to their desired azaindolines (380) is driven by the expulsion of nitrogen gas, a pathway analogous to that of van der Plas’s chemistry.

\textbf{Scheme 148.} Synthesis of 7-Azaindolines via an Inverse Electron Demand Diels-Alder Reaction of Triazines

In 2004, Sanders and colleagues inadvertently discovered that a highly functionalized 2-aminopyridine can be transformed to a 7-azaindole core via a periodinane-mediated formation of a 7-azaindoline scaffold.\textsuperscript{197} Their initial goal was to treat advanced aminopyridine 381 with Dess-Martin periodinane in order to arrive at aldehyde 382, which can then undergo a spontaneous intramolecular aldol cyclization to yield pyrido[2,3-\textit{b}]azepinone 383. Upon exposure to DMP, the primary alcohol of compound 381 was oxidized as expected (Scheme 149). However, the resultant aldehyde did not react with the enol of the ketoester functionality. Instead, what they observed was

\textbf{Scheme 149.} Sanders’s Iodine(III)-Mediated Synthesis of 7-Azaindole 386 via 7-Azaindoline 385

a Friedel-Crafts-type cyclization en route to 7-azaindoline cationic intermediate \(384\). Rearomatization via intermolecular transfer of malonate to a reaction byproduct (not shown) affords a 3-hydroxy azaindoline (\(385\)) that leads to azaindole \(386\) upon dehydration. The proposed cationic intermediate (\(384\)) is exceptionally resonance-stabilized by three nitrogen atoms, and this thermodynamic stabilization combined with the kinetic advantage of five-membered ring formation could explain why the azaindoline moiety was generated in this reaction.

Recently, Sumiyoshi and co-workers utilized an intramolecular nucleophilic aromatic substitution reaction to construct a 7-azaindoline scaffold \((387)\) en route to synthesizing small molecule therapeutic candidates.\(^{198,191}\) Formation of this azaindoline core proceeded in a straightforward manner as commercially available (2-chloro-3-pyridinyl)methanol \(388\) was converted to chloride \(389\) in high yield upon treatment with \(\text{POCl}_3\) (Scheme 150). Nucleophilic displacement of the chloride with cyanide gave \(390\) in 98% yield. Treatment of \(390\) with \(N\)-benzylbis(2-chloroethyl)amine in the presence of base afforded spiropiperidine \(391\) in modest yield. Reduction of the nitrile functionality in compound \(391\) and subsequent exposure to heat promoted the desired \(S_N\text{Ar}\) reaction, providing 7-azaindoline \(387\) in 84% isolated yield. This azaindoline serves as a key scaffold as a multitude of synthetic routes can be pursued in order to arrive at various pharmaceutical candidates.

**Scheme 150.** Sumiyoshi’s Synthesis of a Key 7-Azaindoline Scaffold

One compound of interest was that of \(N\)-sulfonyl-7-azaindoline \(392\). This compound can be delivered via a five-step synthetic sequence from \(387\). Azaindoline \(387\) was converted to intermediate \(393\) by mesylation and debenzylolation (Scheme 151). Free amine \(393\) then underwent reductive amination with \(N\)-Boc-4-formylpiperidine (\(394\)) to afford compound \(395\) in quantitative

yield. Boc-deprotection and subsequent acylation with ethyl chloroformate furnished desired compound 392 in good yield (68% yield over 2 steps). Target compound 374 could also be readily accessed from azaindoline 387 in a highly efficacious manner. Acylation of the free amine moiety with N,N-dimethylcarbamoyl chloride delivered urea 396 in quantitative yield. Debenzylation and reductive amination with ethyl 4-formylpiperidine-1-carboxylate 397 led to the desired target (374) in 86% yield over two steps. These two compounds (392 and 374) showed selective M₁ and M₄ mAChRs agonist activity and are promising antipsychotic candidates with novel mechanisms of action.

Scheme 151. Synthesis of Antipsychotic Candidates 392 and 374

Radical cyclization is another method that can be implemented in order to access the 7-azaindoline backbone. Burgos and colleagues demonstrated this approach when utilizing an intramolecular radical pyridylation en route to synthesizing annulated 2-aminopyridines. Treatment of aminopyridine 398 with AIBN and tris(trimethylsilyl)silane (TTMSS) produced aryl radical 399, which subsequently engaged in a number of mechanistic pathways ultimately generating a series of products (Scheme 152). Isolation of 7-azaindoline 400 (28% yield), suggests that the aryl radical underwent a 5-exo trig cyclization with the terminal alkene. Conversely,

acquisition of tetrahydronaphthyridine 401 (10% yield) indicates that radical 399 proceeded through a 6-endo trig cyclization with the olefin. The main product (402) however, is thought to result from [1,5]-hydrogen transfer followed by a 5-exo trig cyclization (32% yield).

Scheme 152. Burgos’s Synthesis of 7-Azaindoline 400 and Byproducts via Radical Cyclization

Consequently, 403 was prepared in order to suppress the unwanted hydrogen atom transfer process. Under similar cyclization conditions, aryl radical 404 was generated, which gave rise to 7-azaindoline 405 and naphthyridinone 406 via the 5-exo trig and 6-endo trig pathways (Scheme 153). For this particular case, azaindoline 405 was the minor product. Another substrate that was employed in these studies was that of internal alkene 407. When 407 was treated with AIBN and TTMSS, radical 408 was generated subsequently affording 7-azaindoline 409 in 54% isolated

Scheme 153. Radical Cyclizations en Route to 7-Azaindolines 405 and 409
yield. The favorability of the 5-exo trig cyclization for this experiment was thought to be driven by the stabilization of the resulting tertiary radical.

Zard and co-workers were able to effectively synthesize 7-azaindoline cores via radical cyclizations using xanthate esters. As illustrated in their earliest report, treatment of xanthate 410 with stoichiometric quantities of lauroyl peroxide results in the formation of radical 411 (Scheme 154). Propagation of this radical with the pyridine ring generates radical species 412 and subsequent rearomatization furnishes the desired azaindoline (413) in modest yield (42%). This methodology was later extended to the synthesis of 3-alkyl-7-azaindolines (415) as well as fluoro-7-azaindolines (417). These advanced azaindoline scaffolds arose through mechanistic pathways analogous to the one previously described.

Scheme 154. Zard’s Radical-Mediated Synthesis of 7-Azaindolines Using Xanthate Esters

Radical cyclizations with azomethine have also been employed in order to arrive at the 7-azaindoline framework. In 2001, Johnston and colleagues successfully synthesized this bicyclic

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system via an unconventional aryl radical addition to azomethine nitrogen. Herein, amine 418 was condensed with benzophenone to provide azomethine 419 (Scheme 155). Treatment of 419 with AIBN and \(^{t}\)Bu₃SnH at elevated temperatures results in the formation of radical 420. This radical then undergoes a regioselective 5-exo trig cyclization at the nitrogen position of the azomethine yielding 421. Termination of 421 with \(^{t}\)Bu₃SnH affords the desired 7-azaindoline (422) in 50% yield over two steps.

**Scheme 155. Johnston’s Regioselective Synthesis of 7-Azaindoline 422**

Johnston later extended this regioselective aryl radical addition to the synthesis of 7-azaindoline α-amino esters. Subjection of enantioenriched α-amino ester 423 to the radical cyclization protocol afforded the desired 7-azaindoline α-amino ester (426) in 50% yield upon purification (Scheme 156). What is notable about this cyclization is that no diminishment in enantiopurity was observed. This indicates that ring fragmentation and subsequent radical

**Scheme 156. Johnston’s Radical-Mediated Synthesis of 7-Azaindoline 426 with Complete Stereoretention**

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isomerization of the stereocenter does not occur en route to making the azaindoline system. This is unique as the phenyl analog (427) succumbs to loss of ee during the cyclization process, signifying that ring fragmentation and isomerization occurs for this particular substrate. The loss of stereochemical integrity can ultimately be owed to $A^{1,3}$-strain.

After seeing the retention of stereochemistry for the azaindoline system, Johnston and co-workers then applied this free radical-mediated aryl amination to the synthesis of enantiopure 7-azaindoline $\alpha$-amino acids (Scheme 157).\textsuperscript{205,206} Formylation and reduction of commercially available 2-bromopyridine (433) affords compound 434 in modest yield (47% over 2 steps). Treatment of primary alcohol 434 with PBr$_3$ furnishes alkyl bromide 435, which then undergoes a phase transfer-catalyzed glycine alkylation with azomethine 436 to deliver the $R$ and $S$ enantiomers (separately) of 423 in high yield and with high enantioselection. Subjection of both enantiomers of 423 to the 5-exo trig cyclization provides the respective 7-azaindoline $\alpha$-amino esters (426a and 426b) in modest yield and with complete stereoretention. Subsequent deprotection of the tert-butyl ester moiety under acidic conditions generates acid salts 439a and 439b in modest to good yield.

**Scheme 157.** Johnston’s Synthesis of Enantiopure 7-Azaindoline $\alpha$-Amino Acids

Other methods for the synthesis of 7-azaindoline scaffolds include base- and metal-mediated cyclizations. In 2004, Davies and colleagues utilized a directed ortho-


metallation/transmetallation reaction in order to access annulated pyridines. For example, when Boc-protected aminopyridine 440 is treated with 2.2 equivalents of nBuLi in the presence of copper(I) bromide dimethyl sulfide (CuBr•Me₂S) and TMEDA, dianion 441 is formed (Scheme 158). The more reactive anion of species 441 undergoes alkylation with 1-chloro-2-iodoethane to deliver intermediate 442. Subsequent in situ cyclization gave the desired 7-azaindoline (443) in 45% isolated yield.

**Scheme 158. Davies’s ortho-Metallation/Transmetallation Approach to 7-Azaindolines**

![Scheme 158](image)

Shortly thereafter, Nguyen and Wang were able to promote an intramolecular SNAr reaction in the presence of potassium carbonate to furnish 7-azaindoline cores (Scheme 159). Treatment of Boc-protected 1-fluoro-2-alkylamino-3-iodopyridine 444 with TFA afforded the precursor amine, which then succumbed to SNAr upon exposure to K₂CO₃ providing 4-iodo-7-azaindoline 445 in good yield (66% yield over 2 steps). Similarly, subjection of benzyl-protected 1-fluoro-2-alkylamino-3-iodopyridine 446 to K₂CO₃ facilitated the intramolecular cyclization delivering N-benzyl-4-iodo-7-azaindoline 447 in modest yield (55%).

**Scheme 159. Nguyen’s Base-Mediated Synthesis of 7-Azaindolines**

![Scheme 159](image)

As for metal-mediated approaches, Desarbre and Mérour reported a palladium heteroannulation process for the synthesis of 7-azaindolines. To illustrate, aminopyridine 448 was treated with 1-methoxypropadiene (449) and substoichiometric quantities of Pd(PPh₃)₂Cl₂ at elevated temperature to afford 7-azaindoline 450 in 80% yield (Scheme 160). Mechanistically, it is proposed that aminopyridine 448 undergoes palladation followed by π-allylic complexation to arrive at allyl cation 451. With methoxyallene, the methoxy group stabilizes the carbocation at C₁.

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rendering it the most electrophilic position. Regioselective attack by the nitrogen of the amide provides the corresponding azaindoline, consequently.

**Scheme 160.** Mérour’s Palladium Heteroannulation en Route to 7-Azaindolines

![Scheme 160](image)

In 2012, Moss and co-workers employed a one-pot magnesium-mediated ring-opening-cyclization sequence in order to arrive at azaindoline scaffolds.\(^\text{210}\) To demonstrate the efficacy of this process, pyrimidine 452 was subjected to tetramethylpiperidine magnesium chloride lithium chloride complex (TMPMgCl•LiCl) resulting in the formation of magnesiated chloropyrimidine 453 (Scheme 161). This motif can then undergo a facile ring opening with chiral Boc-protected sulfamidate 454 to furnish intermediate 455 upon loss of SO\(_3\). After an acidic workup (removal of the Boc group), this adduct engages in a rapid intramolecular cyclization upon basicification to give highly functionalized stereodefined azaindoline 456 in 85% isolated yield.

**Scheme 161.** Moss’s One-Pot Ring-Opening-Cyclization Sequence en Route to Azaindolines

![Scheme 161](image)

Compared to 7-azaindoline backbones, methods to prepare the 6-azaindoline, 5-azaindoline, and 4-azaindoline congeners are relatively scarce. As for 6-azaindolines, one way to access this bicyclic system is through van der Plas’s inverse electron demand Diels-Alder reaction.\(^\text{211}\) When pyrazine 457 is subjected to high temperature, the intramolecular 4+2 cycloaddition proceeds to provide tricyclic intermediate 458 \textit{in situ} (Scheme 162). Conversion of

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\(^{211}\) de Bie, D. A.; Ostrowicz, A.; Geurtsen, G.; van der Plas, H. C. \textit{Tetrahedron} 1988, 44, 2977-2983.
this cycloadduct (458) to its corresponding 6-azaindoline (459) is driven by the elimination of hydrogen cyanide. The 7-azaindoline analog (460) is also furnished via tricycle 458, but as the minor product.

Dodd and colleagues inadvertently accessed a 6-azaindoline moiety en route to making 6-azaindole-5-carboxylates.212 After successfully synthesizing acyclic acetal 461, this intermediate was subjected to a Pomeranz-Fritsch cyclization using polyphosphoric acid (PPA) and phosphorus oxychloride (POCl3). Aside from furnishing the desired azaindole (462) in 23% yield, 6-azaindoline 463 was also acquired, but as the minor product (Scheme 163). Due to the low yields observed under the Pomeranz-Fritsch protocol, other cyclization conditions were investigated. It was found that refluxing 461 in benzene in the presence of p-toluene sulfonic acid led to an improved overall yield of 462 and 463 (45%). For this particular case, however, 4,5,6,7-tetrahydro-6-azaindole-5-carboxylate derivative 464 was formed as a minor byproduct.

In 2005, Fayol and Zhu reported a highly efficacious three-component synthesis of 6-azaindolines.213 The three substrates employed in this reaction system were that of an isocyanoacetamide, an amine, and an aldehyde. Treatment of morpholine with heptanal and isocyanoacetamide 465 in the presence of toluene at elevated temperature provided polysubstituted 6-azaindoline 466 in modest yield (Scheme 164). Mechanistically, it is envisioned that morpholine

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condenses onto heptanal to deliver iminium 467. Addition of the isocyanacetamide into the iminium yields nitrilium 468. Intramolecular attack of the amide to the nitrilium and subsequent tautomerization/aromatization provides oxazole 469. Interception of the resultant oxazole by the tethered dienophile via an intramolecular Diels-Alder cycloaddition affords oxa-bridge intermediate 470. Dehydration of the oxa-bridge compound leads to the desired 6-azaindoline (466).

**Scheme 164.** Zhu’s Three-Component Synthesis of 6-Azaindolines

For the 5-azaindoline backbone, earliest reports of successfully constructing this bicyclic system include that of Yakhontov and co-workers. Herein, treatment of 3-alkyl-4,6-dichloropyridine 471 with ammonia in ethanol at elevated temperature leads to the formation of 5-azaindoline 472 (Scheme 165). This azaindoline is thought to arise via $S_{N}2$ displacement of the alkyl chloride with ammonia followed by $S_{N}Ar$. Reduction of the aryl chloride with Pd/C and H$_2$ provides 5-azaindoline 473 in 71% yield over 2 steps. Additionally, subjection of 6-hydroxy-5-azabenzo furan 474 to an excess of benzylamine at 190 °C led to benzyl-protected 6-hydroxy-5-

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azaindoline 475 in good yield (72%). Treatment of 475 with POCl₃ converts the hydroxyl motif to a chloride and subsequent deprotection/reduction delivers free 5-azaindoline 473 in quantitative yield.

Scheme 165. Yakhontov’s Synthesis of 5-Azaindolines

Kauffmann and Fischer later reported that base-mediated side chain cyclizations can also be employed in order to access 5-azaindoline cores. Exposure of 3-(2-aminoethyl)-5-bromopyridine 476 to lithium diethylamide not only deprotonates the free amine, it also promotes the formation of benzyne intermediate 477 (Scheme 166). Intramolecular addition of the amine to the benzyne affords the desired 5-azaindoline in moderate yield (56%).

Scheme 166. Kauffmann and Fischer’s Synthesis of 5-Azaindoline 473 via a Benzyne Intermediate

In 1998, Spivey and colleagues successfully synthesized N-methyl-5-azaindoline 478 as a precursor to atropisomeric analogues of DMAP. Beginning with commercially available 4-aminopyridine (479), Boc-protection with (Boc)₂O proceeded well as tert-butyl carbamate 480 was furnished in excellent yield (95%) (Scheme 167). Base-mediated ortho-lithiation of 480 followed by alkylation with ethylene oxide provided alcohol 481 in 75% yield. Mesylation and in situ cyclization delivered N-Boc azaindoline 482 (not shown). This intermediate was then reduced with DIBAL to give 1-methyl-5-azaindoline 483 in modest yield (52% over 2 steps). meta-Bromination with NBS produced bromoarene 484 and the stage was now set for a palladium-mediated Suzuki coupling. Treatment of 484 with 1-naphthylboronic acid (485) in the presence of palladium tetrakis and base delivered atropisomeric DMAP analog 478 in 96% yield. Other

arylboronic acids underwent Suzuki cross couplings with bromoarene 484 to afford a library of DMAP derivatives. These biaryl 5-azaindoline scaffolds were then subjected to acylation reactions in order to test their efficacy as organocatalysts.

Scheme 167. Synthesis of DMAP Analogs via 5-Azaindoline Intermediates

Radical annulations have also been used as a means to access 5-azaindoline cores. In 2008, Wipf and co-workers developed a novel titanocene(III) chloride catalyzed epoxide-opening arene annulation that affords 3,3-disubstituted-5-azaindolines.218 To illustrate, when tethered epoxide 486 is subjected to titanocene(III) chloride in the presence of stoichiometric magnesium metal, Cbz-protected 5-azaindoline 487 is produced (Scheme 168). Subsequent debenzylation delivers

Scheme 168. Titanocene(III)-Catalyzed Formation of 5-Azaindolines

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3,3-disubstituted-5-azaindoline 488 in modest yield (52% over 2 steps). Mechanistically, it is proposed that formation of the β-titanoxy radical 489 is followed by a reversible annulation, which generates aryl radical 490. Oxidative rearomatization affords 491, and protodemetalation by collidinium hydrochloride leads to azaindoline 487 upon the regeneration of the precatalyst Cp₂TiCl₂.

Zard and colleagues utilized xanthate esters in order to promote an unconventional radical-mediated *ipso* substitution en route to generating 5-azaindolines.²¹⁹ For example, treatment of polysubstituted aminopyridine 492 with di-tert-butyl peroxide in the presence of 1,2-dichlorobenzene furnished fluorinated 5-azaindoline 493 in 45% isolated yield (Scheme 169). This azaindoline scaffold was acquired through a mechanistic pathway analogous to the previously reported 7-azaindoline studies.²⁰⁰,²⁰¹,²⁰²

\[ \text{Scheme 169. Zard's Synthesis of 5-Azaindolines Using Xanthate Esters} \]

As for 4-azaindoline scaffolds, few approaches have been reported that provide direct access to this bicyclic system. Among these methods is the use of photochemistry as described by Donati and co-workers.²²⁰ For example, 2-methyloxazolo[5,4-b]pyridine 494 is treated with ethyl vinyl ether in order to promote a photocycloaddition en route to pyridooxazepine 495 (Scheme 170). This unstable intermediate then undergoes hydrolysis to give amide-aldehyde 496. Attack of the amide to the aldehyde generates the more stable 2-hydroxy-4-azaindoline (497) in low yield (23%).

\[ \text{Scheme 170. Synthesis of 4-Azaindoline 497 via Photocycloaddition} \]

Ciufolini and colleagues describe an alkoxyamine-mediated radical synthesis of 4-azaindoline backbones.\textsuperscript{221} Treatment of aminopyridine 498 with alkoxyamine 499 affords 3,3-disubstituted-4-azaindoline 500 in 30\% yield upon chromatographic separation (Scheme 171). Mechanistically, it is postulated that alkoxyamine 499 (a tert-butyl radical source) propagates with the external alkene of 498 resulting in the formation of tertiary radical 501. Propagation of this radical with the pyridine moiety generates radical 502, which later furnishes 4-azaindoline 500 after rearomatization.

\textbf{Scheme 171.} Ciufolini’s Alkoxy-Mediated Radical Synthesis of 4-Azaindolines

As previously mentioned, there is only one known unified approach that readily accesses all four isomeric azaindoline families. In 2008, Bailey and co-workers introduced an intramolecular carbolithiation sequence as a means of synthesizing 3-alkyl 4-, 5-, 6-, and 7-azaindoline backbones.\textsuperscript{192} Precursor substrates were furnished via allylation of aminobromopyridines 503-506 (Scheme 172). The corresponding N,N-diallyl compounds (507-510) were afforded in reproducible yields of 70-90\%. Treatment of substrates 507 and 509 with 2.2 equivalents of t-BuLi in the presence of dry n-pentane-diethyl ether generates the desired aryllithium intermediates. These aryllithium compounds were allowed to stand under argon atmosphere at 0 °C for 2 hours before being quenched with MeOH to provide 1-allyl-3-methyl-4-azaindoline 511 and 1-allyl-3-methyl-6-azaindoline 512 in 80\% and 56\% yields, respectively. When diallyl aminopyridine 510 was subjected to nearly identical reaction conditions, 7-azaindolines 513 and 514 were isolated in 22\% and 70\% yields. The same phenomenon was observed with precursor substrate 508 as 5-azaindoline products 515 and 516 were furnished in low to modest yield (27\% and 43\%). Repetition of the cyclization with substrates 508 and 510

followed by reduction of the crude products delivered 3-methyl-7-azaindoline 518 and 3-methyl-5-azaindoline 517 in 85% and 69% yields, respectively.

**Scheme 172. Bailey’s Unified Approach to All Four Isomeric Azaindoline Families**

6.3. Reaction Optimization and Substrate Scope

Hong and Johnston recently described a new method for the inter-/intramolecular annulative diamination of terminal alkenes via the use of an oxidant/additive combination (Scheme 173). Treatment of tosylated vinylaniline (327) with PhI(OAc)$_2$, KI, and a broad range of electron-rich amines effectively delivered a library of 3-aminoindolines without the need for amine preactivation and protection. This approach displayed a high degree of generality as both mono- and disubstituted amines were successfully converted to their respective indoline products.
Based on the success of the aforementioned reaction system, we sought to extend this methodology to the synthesis of all four azaindoline heterocycle families. The goal was to convert four isomeric vinylpyridine substrates to their corresponding 3-amino azaindoline scaffolds via a hypervalent iodine-/iodide-mediated inter-/intramolecular annulative diamination, an approach analogous to that of Hong and Johnston’s (Scheme 174). Introduction of pyridine-derived starting materials provides an opportunity to evaluate the compatibility of Lewis basic pyridine nitrogens with the oxidative, electrophilic (I+) conditions.

Scheme 174. Inter-/Intramolecular Diamination of Vinylpyridines en Route to All Four Azaindoline Families

The first substrate to be examined was that of 3-vinyl-2-tosylaminopyridine (519). Acquisition of this starting alkene was straightforward as commercially available 2-amino-3-bromopyridine (506) was subjected to a Stille coupling with tributyl(vinyl)tin to afford free vinyl aminopyridine 520 in 90% yield upon chromatographic separation (Scheme 175). Subsequent tosylation of 520 under basic conditions and at elevated temperature gave 3-vinyl-2-tosylaminopyridine (519) in 23% isolated yield.
With vinyl aminopyridine 519 in hand, the stage was now set for reaction optimization. Electrophilic iodinating reagents were the first variant to be examined. When NIS was employed as the iodinating agent in the presence of vinylpyridine 519 and aniline (the amine source), 3-amino-7-azaindoline 521a was provided but in low yield (Table 23, entry 1). When the iodonium source was generated through PhI(OAc)2 and KI, the desired azaindoline was furnished in 96% isolated yield, once again proving the superiority of the oxidant/additive combination (Table 23, entry 2). Use of tetrabutylammonium iodide as the halide source proved slightly inferior as azaindoline 521a was afforded in 80% yield (Table 23, entry 3). Ammonium iodide further mitigated reactivity as 521a was acquired in only 29% yield (Table 23, entry 4). Use of both components of the oxidant/additive combination proved vital, as no conversion to product was observed when starving the reaction conditions of either the oxidant or the halide additive (Table 23, entries 5-7). Catalytic quantities of iodide proved effective as 30 mol% and 50 mol% loadings of KI led to 63% and 65% isolated yields of azaindoline 521a, respectively (Table 23, entries 8-9). Despite the success seen with substoichiometric amounts of halide, stoichiometric quantities were necessary as they provided the most fruitful results.

Table 23. Initial Optimization Studies of the Inter-/Intramolecular Annulative Diamination

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>oxidant equiv</th>
<th>additive</th>
<th>additive equiv</th>
<th>conversion (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NIS</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>PhI(OAc)2</td>
<td>1.5</td>
<td>KI</td>
<td>1.0</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>PhI(OAc)2</td>
<td>1.5</td>
<td>tBuNi</td>
<td>1.0</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>PhI(OAc)2</td>
<td>1.5</td>
<td>NH4I</td>
<td>1.0</td>
<td>77</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>PhI(OAc)2</td>
<td>1.5</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>tBuNi</td>
<td>1.0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>KI</td>
<td>1.0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>PhI(OAc)2</td>
<td>1.5</td>
<td>KI</td>
<td>0.3</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>PhI(OAc)2</td>
<td>1.5</td>
<td>KI</td>
<td>0.5</td>
<td>88</td>
<td>65</td>
</tr>
</tbody>
</table>

With optimum reactivity achieved, the next goal was to expand the 3-amino-7-azaindoline library. Monosubstituted aliphatic amines in benzylamine and allylamine successfully engaged in diamination as 3-amino-7-azaindoline products 521b and 521c were afforded in 73% and 62% yields, respectively (Table 24, entries 2-3). Heterocyclic disubstituted amines were also tolerated.
as thiomorpholine and morpholine delivered their corresponding azaindolines (521d and 521e), albeit in depressed yields (39% and 57%) (Table 24, entries 4-5).

Table 24. 3-Amino-7-Azaindoline Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>521</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Ph (aniline)</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>CH₂Ph (benzylamine)</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>CH₂CHCH₂ (allylamine)</td>
<td>62</td>
</tr>
<tr>
<td>4a</td>
<td>d</td>
<td>C₄H₈S (thiomorpholine)</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>C₄H₈O (morpholine)</td>
<td>57</td>
</tr>
</tbody>
</table>

a2.0 equiv of Ph(OAc)₂, 1.2 equiv of KI, 3.0 equiv of amine used

Efforts then shifted towards generating a 3-amino-6-azaindoline library from vinyl aminopyridine 522. Synthesis of this vinylpyridine substrate was initiated when commercially available 3-amino-4-bromopyridine (505) was treated with tosyl chloride in the presence of KHMDS to afford tosylated bromopyridine 523 in 34% yield (Scheme 176). Intermediate 523 was then subjected to a palladium-mediated Stille coupling with tributyl(vinyl)tin at elevated temperature to provide 4-vinyl-3-tosylaminopyridine 522 in modest yield (41%).

Scheme 176. Synthesis of Vinyl Aminopyridine 522

This vinylpyridine substrate (522) was then treated with aromatic, primary, and secondary amines in order to generate a series of 6-azaindoline scaffolds. Aniline and benzylamine proved tolerant in this system as the desired 3-amino-6-azaindoline products (524a and 524b) were furnished in 11% and 48% yields, respectively (Table 25, entries 1-2). Furthermore, Cbz-, Boc-, and ethyl carboxylate-protected piperazines were readily converted to their corresponding 6-azaindolines (524c-524e) with good yields (Table 25, entries 3-5). These three diamines are notable as they allow for subsequent unmasking of the piperazine moiety under neutral, acidic, or basic conditions.
Our focus then centered upon successfully generating the 5-azaindoline congener. Vinyl aminopyridine 525, the precursor to 5-azaindoline diamines, was synthesized via a pathway analogous to those of the 7-azaindoline and 6-azaindoline precursor substrates. 4-Amino-3-bromopyridine (504) underwent tosylation with KHMDS, providing intermediate 526 in 51% yield post column chromatography (Scheme 177). This tosylated amino bromopyridine was then subjected to a Stille coupling with tributyl(vinyl)stannane in order to arrive at vinylpyridine 525 in low yield (15%).

**Scheme 177. Synthesis of Vinyl Aminopyridine 525**

This vinyl aminopyridine (525) proved to be an effective substrate as it was compatible with a wide array of amines. Aniline performed well under optimal conditions, as 5-azaindoline product 527a was furnished in 81% yield (Table 26, entry 1). Benzyamine and derivatives were converted to 3-amino-5-azaindolines 527b-527d in 43-51% yield (Table 26, entries 2-4). Alkyl amines including 3-methoxypropylamine and phenethylamine performed similarly (Table 26, entries 5-6). Other primary amines such as 4-amino tetrahydropyran and 3-picolylamine delivered their corresponding 3-amino-5-azaindolines (527g and 527h) in 33% and 64% yields respectively, when subjected to the reaction protocol (Table 26, entries 7-8). A secondary amine in thiomorpholine also engaged in dimation as 5-azaindoline 527i was afforded, albeit in lower yield (Table 26, entry 9).

### Table 25. 3-Amino-6-Azaindoline Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>524</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Ph (aniline)</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>CH₂Ph (benzylamine)</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>R' = Cbz</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>R' = CO₂Et</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>R' = Boc</td>
<td>74</td>
</tr>
</tbody>
</table>

144
The next objective was to apply this inter-/intramolecular annulative diamination protocol towards the synthesis of 3-amino-4-azaindolines and consequently confirm that all four isomeric azaindoline families could be readily accessed. Synthesis of 2-vinyl-3-tosylaminopyridine (528) proceeded in a straightforward manner as tosylation of commercially available 3-amino-2-bromopyridine (503) delivered tosylated bromopyridine 529 (Scheme 178). This compound, carried on quantitatively, underwent a Stille coupling with tributyl(vinyl)tin in order to generate vinyl aminopyridine 528 in 37% yield over two steps.

Scheme 178. Synthesis of Vinyl Aminopyridine 528

Development of the 4-azaindoline library was straightforward and suitable with aromatic, primary, and secondary amines. Aniline and 4-tert-butyl aniline were successfully converted to their corresponding 3-amino-4-azaindolines (530a and 530b) in 70% and 41% yields, respectively (Table 27, entries 1-2). Benzylamine performed well as its 4-azaindoline (530c) was provided in good yield (Table 27, entry 3). Other primary amines in the form of cyclopentylamine and phenethylamine also engaged in diamination as vicinal diamines 530d and 530e were afforded in 59% and 68% yields (Table 27, entries 4-5). Disubstituted amines in piperidine and ethyl isonipecotate proved compatible under optimal conditions as 4-azaindoline diamines 530f and 530g were isolated in modest to good yields (Table 27, entries 6-7). N-Protected piperazines led

<table>
<thead>
<tr>
<th>entry</th>
<th>527</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Ph (aniline)</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>CH₂Ph (benzylamine)</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>n-C₅H₄CH₂CH₂ (4-methylbenzylamine)</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>FC₆H₄CH₂ (4-fluorobenzylamine)</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>(CH₃)₂O (3-methoxypropylamine)</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>CH₃CH₂CH₃ (phenethylamine)</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>C₆H₅CH₂ (4-aminotetrahydropyran)</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>³CH₃C₆H₅N (3-picolyamine)</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>CH₂H₂S (thiomorpholine)</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 26. 3-Amino-5-Azaindoline Scope
to 3-amino-4-azaindolines 530h and 530i in good yields, allowing for subsequent unmasking of the piperazine under both basic and acidic conditions (Table 27, entries 8-9). Further success with piperazines was demonstrated when N-cinnamyl piperazine delivered 3-amino-4-azaindolone 530j in 66% isolated yield (Table 27, entry 10). Lastly, the HCl salt of glycine methyl ester underwent annulative diamination as 4-azaindolone 530k was furnished in moderate yield (Table 27, entry 11). For this particular case, K$_2$CO$_3$ was incorporated in the reaction system with the sole purpose of liberating the free base of the glycine methyl ester. This modification had little or no effect on reaction progression as azaindolone 530k could be cleanly isolated in a straightforward manner. This entry demonstrates that amino acid derivatives can be readily incorporated into azaindolone motifs.

### Table 27. 3-Amino-4-Azaindolone Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>530</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Ph (aniline)</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>4-tBu-C$_6$H$_4$</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>CH$_2$Ph (benzylamine)</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>C$_6$H$_5$ (cyclopentylamine)</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>CH$_2$CH$_2$C$_6$H$_5$ (phenethylamine)</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>C$_5$H$_10$ (piperidine)</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>C$_6$H$_7$O$_2$ (ethyl isonipecotate)</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>R' = CO$_2$Et</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>R' = Boc</td>
<td>74</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>R' = CH$_2$CHCHC$_6$H$_5$</td>
<td>66</td>
</tr>
<tr>
<td>11$^a$</td>
<td>k</td>
<td>CH$_2$COOCH$_3$•HCl (glycine methyl ester•HCl)</td>
<td>63</td>
</tr>
</tbody>
</table>

$^a$2.0 equiv of K$_2$CO$_3$ used.

### 6.4. Mechanistic Hypothesis

A mechanistic hypothesis is depicted in Figure 30. It is believed that electrophilic iodinating agent A is generated upon the interaction of PhI(OAc)$_2$ with KI. Attack of iodane A with nucleophilic amine results in the formation of iodamine B. Association of B with the alkene moiety of vinylpyridine C leads to aziridinium D. This intermediate (D) then succumbs to intramolecular cyclization via nucleophilic attack of the tosylated amine at the least-hindered position of the aziridinium ring to yield the desired azaindolone product (E).
6.5. Future Work

Based on the high degree of success observed with this annulative diamination, there are several directions that can be pursued in order to make this system more efficacious. One pathway to explore would be the extension of this methodology to the synthesis of 3-alkyl-3-aminoazaindolines (Scheme 179). If α-alkylated vinyl pyridines can successfully engage in the PhI(OAc)$_2$/KI-mediated annulative diamination, this would give rise to azaindoline products bearing tetrasubstituted carbons. Not only would this approach be seen as a novel method to prepare heterocycles with quaternary carbon centers, these scaffolds may also garner interest as they can serve as structural cores for compounds of medicinal importance.

Scheme 179. Proposed Synthesis of 3-Alkyl-3-Amino-Azaindolines

The enantioselective variation of this inter-/intramolecular alkene diamination is another route to be taken. This can be probed by subjecting a number of chiral organocatalysts (e.g. PBAM) to the previously developed protocol (Scheme 180). Application of chiral hypervalent iodine reagents, as described by Muñiz and Ishihara, is another plausible approach that could readily achieve enantioselection. If the use of organocatalysts and/or transition-metal-free methods prove
fruitless, transition-metal catalysis can also be employed in order to induce enantioselectivity. Due to the evidence of halamine formation, it is feasible for a transition metal to oxidatively add between the nitrogen-iodine bond and have a chiral bidentate ligand (e.g. Box ligand) promote enantioselection via coordination to the metal-halamine complex. These investigations are currently ongoing within our laboratory.

Scheme 180. Potential Enantioselective Variation of the Annulative Diamination
Chapter 7. Efforts Towards the Enantioselective Synthesis of Sesbanine: A Potential Antileukemic

7.1. Background

Leukemia is a type of cancer of the blood or bone marrow that is characterized by the uncontrolled proliferation and accumulation of leukocytes (i.e. white blood cells). As there are many different types of leukocytes, there can be many different forms of leukemia. The four most important forms of leukemia, however, are derived from only two types of cells.\(^{222}\)

Acute and chronic lymphocytic leukemias constitute two of the four important forms of this cancer. Lymphocytic leukemia results from malignancies of lymphocytes, which are cells produced in the lymphoid organs (i.e. the spleen, lymph nodes, and thymus) and in the bone marrow. Acute and chronic myelogenous leukemias make up the other two important forms of this cancer. Myelogenous leukemias (also known as myelocytic leukemias) are disorders of granulocytes. Granulocytes, a category of white blood cells produced by bone marrow, are responsible for engulfing and digesting bacteria as well as other small particles.\(^{222}\)

Acute leukemias typically appear suddenly, with symptoms like those of a cold, and progress rapidly. Upon progression, the lymph nodes, spleen, and liver may become infiltrated with leukocytes and enlarged. Additional symptoms may include bone pain, paleness, a tendency to bleed easily, and a high susceptibility to infections. Immediate treatment of acute leukemias is necessary as failure to treat these types may result in death in as little as three months after onset.\(^{222}\)

Chronic leukemias, however, begin much more slowly. Many cases are discovered during routine blood examinations, and several years may pass before significant symptoms appear. Although the symptoms of chronic leukemias are similar to those of acute leukemias, patients with the chronic types can live as long as three years after onset without having to undergo any form of treatment.\(^{222}\)

Leukemia can affect people of all ages, and can be a considerably fatal disease if not treated properly. A World Health Organization study conducted in 2000 estimated that 255,932 children and adults around the world had developed some form of leukemia, and 209,328 have died from it indicating an 82% mortality rate.\(^{223}\) It is also known that certain types of leukemia are more

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prominent in select stages of life. Acute lymphocytic leukemia (ALL), for example, is the most common type of childhood cancer, accounting for approximately one-third of all childhood neoplasms in developed countries.\textsuperscript{224,225} It is estimated that 2,900 children and adolescents under age 20 are diagnosed with ALL each year. It is most common in younger children, especially children ages two and three. The five-year survival rate of children with ALL is 85% for children younger than 15 and 50% for teens aged 15 to 19.\textsuperscript{225}

**Figure 31.** Chemotherapeutic Agents Used in the Treatment of Acute Lymphocytic Leukemia (ALL)

Conversely, chronic lymphocytic leukemia (CLL) is the most common type of leukemia among adults in the western world. The incidence of CLL in the United States alone is approximately 3.9 cases per 100,000 inhabitants, and the median age of diagnosis is 72. The clinical course of CLL is heterogeneous and survival times range from a few years to several


decades. However, approximately 5 to 20% of CLL patients develop Richter’s syndrome, an aggressive lymphoma, which results in a short survival time.\(^{226}\)

A variety of methods are used to treat leukemia, the most common being chemotherapy. The combinations of drugs used in chemotherapeutic treatments are ultimately dependent upon the type of leukemia present in the patient. For patients diagnosed with ALL, the first combination of drugs to be used successfully for induction chemotherapy included vincristine and corticosteroids, most often prednisone. Forty to sixty percent of patients treated with this combination achieved complete remission, although the median remission duration was only three to seven months. Anthracyclines, such as doxorubicin and daunorubicin, were later incorporated into this combination, and the complete remission rate rose from 47% to 85%. Other chemotherapeutic agents have been incorporated into induction regimens to improve results including cyclophosphamide, L-asparaginase, cytarabine, etoposide, teniposide, and amsacrine (Figure 31). Though these agents proved effective in treating ALL, the overall results seem to be equivalent to those with vincristine, anthracyclines, and corticosteroids.\(^{227}\)

**Figure 32.** Purines and Other Agents Used in the Treatment of Chronic Lymphocytic Leukemia (CLL)

For consolidation chemotherapy, the use of high dose methotrexate, sometimes in combination with 6-mercaptopurine (6MP) or with teniposide and cytarabine, and asparaginase has significantly contributed to a cure rate of 70-80% among children with ALL (Figure 31). As for adults however, some reviews concluded that consolidation chemotherapy has not improved


results, whereas others disagreed. Maintenance chemotherapy has proven valuable, especially in cases of childhood ALL. Similar to consolidation chemotherapy, this therapy is usually given with 6MP and methotrexate and is continued for 2 years.\(^{227}\)

Patients diagnosed with CLL are typically subjected to purine-based chemotherapeutic treatments. Three purine analogues are currently used in CLL chemotherapy: fludarabine, pentostatin, and cladribine. Fludarabine remains by far the best studied compound of the three in CLL, and fludarabine monotherapy produces superior overall response rates compared with other treatment regimens containing alkylating agents or corticosteroids. Additionally, it has been demonstrated that fludarabine induces more remissions and more complete remissions than other conventional chemotherapies, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone), or chlorambucil (Figure 32). Though fludarabine has proven to be a powerful therapeutic, chemotherapy for CLL is not limited to monotherapy with purine analogues. A number of monoclonal antibodies have been approved and can be used in combination with fludarabine. Some monoclonal antibodies include alemtuzumab, ofatumumab, and rituximab (Figure 33). The most thoroughly studied combination chemotherapy for CLL is fludarabine plus cyclophosphamide (FC). In preliminary, non-comparative trials, the overall response rates did not improve relative to using fludarabine alone. However, the addition of cyclophosphamide appeared to improve the quality of responses.\(^{228}\)

Additional studies have also confirmed that fludarabine and cyclophosphamide (FC) have achieved complete remission in approximately 24% to 39% of patients. Yet when introducing the monoclonal antibody rituximab to fludarabine and cyclophosphamide (FCR), the complete remission rates rose to 70% in chemotherapy-naïve patients. Thus, incorporation of a monoclonal antibody in CLL chemotherapy yields vast improvements.\(^{229}\)

Myelogenous leukemias are treated with a much smaller range of chemotherapeutic agents. Patients diagnosed with acute myelogenous leukemia (AML) are often subjected to a “3+7” induction chemotherapy regimen. This “3+7” therapy consists of treating the patient with an anthracycline (most commonly daunorubicin) for 3 days followed by a 7-day treatment with cytarabine. These “3+7” regimens have proven effective as complete remission is achieved in 60%.

\(^{228}\) Hallek, M. *Hematology* 2005, 1, 285-291.

Patients diagnosed with chronic myelogenous leukemia (CML) are often treated with imatinib (also known as Gleevec) (Figure 34). Imatinib is effective as a single agent for the treatment of patients in all stages of CML, with the most encouraging results seen in patients in chronic phase disease. Hematologic and cytogenetic responses to imatinib for the treatment of chronic phase CML have permitted imatinib to be registered as the first-line treatment for newly diagnosed CML.\(^{231}\)

Figure 34. Agents Used in the Treatments of Acute and Chronic Myelogenous Leukemias (AML and CML)

Although it has been shown that a number of clinically effective drugs can treat leukemia, there are other agents that have shown promising antileukemic activity as well. Amongst these agents is sesbanine, a novel alkaloid compound that has been produced from the tissue of a leguminous plant known as *Sesbania drummondii* (commonly known as coffeebean, rattle bush, or rattle box).\(^{232,233}\) First isolated by Powell and colleagues in 1979, sesbanine and other members

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of *Sesbania drummondii* are significantly active against lymphocytic leukemia P-388 *in vivo*.\(^{234,235,236}\) Along with its potential as an antileukemic, sesbanine also possesses a unique structural composition. Structural elucidation shows that this molecule has a previously unreported and highly unusual spirocyclic structure based on the 2,7-naphthyridine framework (Figure 35).\(^{234}\) With the combination of its potent antileukemic activity and unconventional structure, sesbanine serves as an attractive target for organic synthesis.

![Figure 35. Structure of Sesbanine](image)

7.2. Previous Syntheses of Sesbanine

A number of stereospecific and stereoselective syntheses of sesbanine have previously been reported in literature. These approaches are highly efficacious as the desired alkaloid can be successfully furnished within five to eight synthetic steps. Furthermore, these syntheses feature a variety of key reactions that ultimately facilitate the access of sesbanine.

In 1980, Kende and Demuth reported a stereospecific synthesis of sesbanine (531) utilizing a key cycloannellation reaction.\(^{237}\) Beginning with 4-methylnicotinonitrile (532), a direct carbothoxylation reaction with diethyl carbonate and NaHMDS provided cyanoester 533 in 40% yield, setting the stage for the key cycloannellation step (Scheme 181). Treatment of 533 with 1,2-epoxy-4-bromobutane in the presence of absolute ethanol and K\(_2\)CO\(_3\) afforded cyclopentanol product 534 as a single racemic diastereomer (40-45% yield). Further experimentation and characterization determined that 534 was indeed the undesired *cis*-stereoisomer. To account for the incorrect stereochemistry, the free alcohol of compound 534 was tosylated furnishing tosylate 535 in 67% yield. Nucleophilic displacement of the tosylate with tetraethylammonium acetate and subsequent mild hydrolysis gave cyclopentanol 536 in good yield (83% over 2 steps) and with the

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desired stereochemistry. The synthesis was completed when cyclopentanol 536 underwent a mild hydrolytic cyclization to arrive at sesbanine (531) in 60% yield.

**Scheme 181. Kende and Demuth’s Stereospecific Synthesis of Sesbanine**

Shortly after the publication of Kende and Demuth’s synthesis, Tomioka and Koga described their respective synthesis of sesbanine, which utilized a very similar approach.238,239 4-methylnicotinonitrile was converted to cyanoester 533 via an alkoxy carbonylation reaction with diethyl carbonate and NaH (Scheme 182). When 533 underwent cycloannelation with racemic 1,4-dibromobutan-2-ol, cyclopentanol 534 was provided, but only as the cis-stereoisomer. Because of the selectivity for the cis-isomer, optically active 1,4-dibromobutan-2-ol (537) was later employed in the key cycloannelation step delivering cyclized product 534 in 27% yield. The stereoinversion of the hydroxyl group in compound 534 was achieved via a Mitsunobu reaction affording acetate 538 in high yield (91%). Cleavage of the acetate moiety under basic conditions furnished desired alcohol 536 in 98% yield. Treatment of 536 with alkaline hydrogen peroxide in aqueous ethanol promoted a cyclic-imide formation to give sesbanine (531) in modest yield (67%).

**Scheme 182. Tomioka and Koga’s Synthesis of Sesbanine**

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In 1983, Iwao and Kuraishi reported the synthesis of sesbanine via the directed metalation of tertiary nicotinamides. This synthetic route was initiated when readily available \( N,N \)-diisopropyl nicotinamide (539) was selectively lithiated at the 4-position with LiTMP to provide lithiated species 540 (not isolated) (Scheme 183). Condensation of 540 with 3-cyclopentenone and subsequent treatment with TFA afforded spirolactone 541 (63% yield over 3 steps). Lactone 541 was reductively cleaved with zinc-copper couple to give acid 542 in 94% yield. This acid was once again lithiated with LiTMP, generating dianion 543. This dianionic species was then carboxylated with dry ice, neutralized with methanolic HCl, and subsequently treated with freshly prepared diazomethane to furnish diester 544 in 52% yield over the course of 3 steps. Treatment of 544 with NBS in aqueous DMSO gave bromohydrins 545 and 546 in 38% and 21% yields, respectively. Both bromohydrins were converted to their corresponding alcohols (547 and 548) via a reductive dehalogenation with \( \text{Bu}_3\text{SnH} \) and AIBN. The undesired alcohol (547) was epimerized to desired alcohol 548 via a Mitsunobu reaction and subsequent hydrolysis of the acetate functionality (85% yield).

Scheme 183. Iwao and Kuraishi’s Synthesis of Sesbanine

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yield over 2 steps). Alcohol 548 was successfully converted to sesbanine in 80% yield upon heating in methanolic NH₃.

Pandit, Wanner, and Koomen demonstrate that the condensation of a carboxylate ester with N-benzynicotinamide can serve as a viable approach in order to arrive at sesbanine.²⁴¹,²⁴² Known methyl 3-oxocyclopentanecarboxylate (549) was converted to acetal 550 in 92% yield upon treatment with ethylene glycol under acidic conditions (Scheme 184). 550 was then deprotonated with LDA, and the corresponding anion was allowed to react with N-benzynicotinamide 551 in order to provide tricyclic system 552 after workup. The dihydropyridine ring of 552 was oxidized with N-benzyquinolinium bromide in acetonitrile, and the resulting pyridinium salt was debenzylated by heating under vacuum. Subsequent deprotection of the acetal moiety furnished sesbanine precursor 553 in modest yield (44% over 3 steps). Ketone 553 was then subjected to a Meerwein-Ponndorf-Verley reduction with Al(OiPrO)₃ affording a mixture of sesbanine (531) and epi-sesbanine (554) in a 6:1 ratio (58% yield).

Scheme 184. Pandit, Wanner, and Koomen’s Synthesis of Sesbanine

Wada, Nishihara, and Akiba later describe a synthesis of sesbanine that utilizes a regioselective γ-addition of a silyl enol ether into a quaternized methyl nicotinate.²⁴³ Treatment of commercially available methyl nicotinate with methyl chloroformate generates a pyridinium salt, which is then condensed in situ with the ketene silyl acetal of methyl 3-cyclopentenecarboxylate

to provide compound 556 (Scheme 185). Subsequent oxidation of 1,4-dihydropyridine 556 with DDQ furnished diester 544 in good yield (77% over 3 steps). Subjection of diester 544 to an oxymercuration protocol delivered alcohols 547 and 548 upon careful reduction with NaBH₄. Fortunately, the desired alcohol (548) was obtained stereoselectively in 64% yield along with undesired epimeric alcohol 547 (7% yield). Imide formation en route to sesbanine was successfully achieved in 86% yield when 548 was heated in methanolic HCl at 100 °C in a sealed tube.

Scheme 185. Wada, Nishihara, and Akiba’s Synthesis of Sesbanine

Bottaro and Berchtold employ a key halolactonization reaction in their respective synthesis of racemic sesbanine.²⁴⁴ Beginning with known 4-(methoxycarbonyl)nicotinic acid, reduction with LiAlH₄ and subsequent treatment with PCl₅ led to chloromethyl acyl chloride 558 (Scheme 186). Methanolysis of the acyl chloride and nucleophilic displacement of the alkyl chloride with NaCN delivered cyanoester 559 in 19% yield over the course of 4 steps. Cyanoester 559 then underwent an inter/intramolecular bis-substitution reaction at the benzylic position with (Z)-1,4-dichlorobut-2-ene providing intermediate 560 in modest yield (42% yield). With intermediate 560 in hand, the stage was now set for the stereospecific iodolactonization step. Ester 560 was saponified with base generating the precursor acid (not isolated). The resulting saponification mixture was immediately treated with I₂, KI, and NaHCO₃ in order to promote the halolactonization in situ. Upon isolation of the desired iodolactone (561), this compound underwent reductive dehalogenation with n-Bu₃SnH and AIBN, furnishing lactone 562 (not shown) in satisfactory yield (60% yield over 3 steps). Aminolysis of lactone 562, intramolecular addition of the amide anion to the nitrile group,

and hydrolysis to the imide via aqueous workup afforded racemic sesbanine in good yield (70% yield over 3 steps).

**Scheme 186.** Bottaro and Berchtold’s Synthesis of Sesbanine

7.3. Initial Efforts Towards the Enantioselective Synthesis of Sesbanine

The use of a halolactonization reaction in Bottaro and Berchtold’s synthesis of sesbanine garnered interest as similar chemistry has been pursued within our laboratory. Recently, Dobish and Johnston employed a chiral proton catalyst-N-iodosuccinimide (NIS) reagent system to facilitate highly enantioselective iodolactonizations of alkenes.\(^{245}\) Herein, the triflimide salt of a chiral stilbene diamine-derived bis(amidine) organocatalyst (StilbPBAM•HNTf\(_2\), 88•HNTf\(_2\)) promotes the transformation of a broad range of unsaturated carboxylic acids to their corresponding γ-lactones in high yields and with excellent levels of enantioselection (Scheme 187). Based on this success and on Bottaro and Berchtold’s synthesis, we saw this as an opportunity to achieve two primary objectives: 1) to extend this methodology to carboxylic acids bearing internal Z-alkenes and 2) to apply this system towards an enantioselective synthesis of sesbanine.

Retrosynthetically, the endgame strategy for our respective synthesis will be identical to that of Bottaro and Berchtold’s. Sesbanine (531) can arise from intermediate 563 through a base-promoted addition of the amide functionality to the nitrile motif followed by acid-mediated hydrolysis (Scheme 188). Amide 563 can be provided via reductive dehalogenation and subsequent aminolysis of iodolactone 561. We can then arrive at this iodolactone upon subjection

of precursor acid 564 to an enantioselective, BAM-catalyzed halolactonization. Nucleophilic aromatic substitution between cyclopentene carbonitrile 565 and methyl nicotinate 566 will deliver ester 560, which in turn can be saponified to give acid 564. Carbonitrile 565 will be afforded from ethyl cyanoacetate (567) via substitution and decarboxylation, and nicotinate 566 can be synthesized upon acylation with the acid chloride of nicotinic acid 568.

In the forward sense, treatment of commercially available ethyl cyanoacetate 567 with (Z)-1,4-dichlorobut-2-ene under basic conditions promoted the desired inter/intramolecular bis-substitution reaction as cyclopentene compound 569 was furnished in 99% yield after chromatographic purification (Scheme 189). Subsequent decarboxylation of 569 with sodium...
chloride (NaCl) in DMF at high temperature delivered the cyclopentene carbonitrile nucleophile (565) in modest yield upon vacuum distillation (44%).

Synthesis of the electrophilic species for the proposed S_NAr reaction proceeded in a straightforward manner. Treatment of 4-chloronicotinic acid 568 with SOCl_2 provided acid chloride 570 quantitatively (Scheme 190). Immediate exposure of 570 to methanol in the presence of base facilitated esterification to give methyl nicotinate 566 in 82% yield. With carbonitrile 565 and nicotinate 566 in hand, the stage was now set for nucleophilic aromatic substitution. After several attempts, it was found that subjection of carbonitrile 565 to a solution of KHMDS in THF promoted nucleophilic attack as S_NAr product 560 was cleanly furnished upon incorporation of the nicotinate electrophile. It is worth noting that nicotinate 566 was chosen as the electrophile since S_NAr attempts with nicotinic acid 568 proved fruitless. The inability to isolate carboxylic acid 564 (if formed in situ) may be owed to the fact that it is too water soluble to withstand an aqueous work-up. Therefore, it was deemed necessary to use nicotinate 566 since the corresponding substitution product (560) will have a lower affinity for the aqueous layer relative to 564.

Scheme 190. Acquisition of Nicotinate 566 and S_NAr en Route to Ester 560

After successfully acquiring ester 560, the next goal was to isolate acid 564 as its own entity. Ester 560 was subjected to a saponification protocol using sodium hydroxide (NaOH), methanol, and water. Aqueous acidic work-up delivered a compound in which the ^1_H NMR data

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was consistent with that of desired acid 564. However, when analyzing the IR spectrum for this compound, no absorption band corresponding to a nitrile motif could be found. Further data evaluation determined that the isolated intermediate was that of spirocyclic imide 571 (Scheme 191). Since this imide was obtained in only 17% yield, it is plausible that the desired acid (564) was formed \textit{in situ} but resisted isolation since the pyridine and carboxylic acid moieties increase water solubility.

\textbf{Scheme 191. Isolation and Confirmation of Imide 571}

\begin{center}
\includegraphics[width=\textwidth]{Scheme191.png}
\end{center}

To account for the potential water solubility of the pyridine ring, carbonitrile 565 and methyl-2-chlorobenzoate (572) were subjected to the S\textsubscript{N}Ar protocol with ambitions of accessing compound 573 (not shown), the phenyl analog of ester 560. Interestingly, when the cyclopentene carbonitrile was treated with KHMDS (1 M in THF) and benzoate 572, iminopiperidinone 574 was the only compound that could be cleanly isolated (Scheme 192). Acquisition of this intermediate not only indicated that S\textsubscript{N}Ar was successful, it also showed that amidation and addition to the nitrile functionality occurred as well. To further confirm that this structure was indeed an imidopiperidinone, 574 was treated with NaOH in the presence of aqueous methanol to provide imide 575 in good yield upon hydrolysis of the imine.

\textbf{Scheme 192. Acquisition and Confirmation of Imidopiperidinone 574}

\begin{center}
\includegraphics[width=\textwidth]{Scheme192.png}
\end{center}

Since the isolation of acid 564 and ester 573 proved troublesome, the next avenue that was explored was a one-pot saponification-iodolactonization reaction. Bottaro and Berchtold utilized this approach by treating ester 560 with NaOH in aqueous methanol providing acid 564 \textit{in situ}. Immediate incorporation of iodine, iodide, NaHCO\textsubscript{3}, and DCM in water promoted the biphasic halolactonization reaction, and the desired iodolactone was successfully isolated. When this one-pot reaction was repeated within our laboratory, the desired lactone (561) was acquired but in very
low yield (3%) (Scheme 193). Nevertheless, this was an opportunity to see if our Brønsted basic BAM catalysts could promote reactivity and induce enantioselection in this one-pot saponification-lactonization system.

**Scheme 193. Repetition of Bottaro and Berchtold’s One-Pot Saponification-Iodolactonization**

![Scheme 193](image)

Initial investigations of this enantioselective saponification-iodolactonization reaction consisted of using the same saponification conditions as described by Bottaro and Berchtold. For the halolactonization stage, the same reagents were used with the exception of replacing NaHCO₃, an achiral base, with PBAM, a Brønsted basic chiral organocatalyst. When substoichiometric amounts of PBAM (19) were employed in this reaction system, no desired lactone could be detected as small quantities of the starting ester were recovered (Table 28, entry 1). The reaction conditions were further modified when NIS replaced the I₂-KI combination as the iodine source. Unfortunately, this variation also proved fruitless (Table 28, entry 2). Substituting the DCM-H₂O solvent combination with toluene showed no improvement as no product was seen even at elevated temperatures (Table 28, entries 3 and 4). Additionally, stilbene diamine-derived organocatalyst StilbPBAM (88) was subjected in lieu of PBAM, but to no avail (Table 28, entry 5).

**Table 28. Initial Investigations of the Enantioselective Saponification-Iodolactonization Reaction**

<table>
<thead>
<tr>
<th>entry</th>
<th>iodine source</th>
<th>additive</th>
<th>catalyst</th>
<th>solvent</th>
<th>T (°C)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂</td>
<td>KI</td>
<td>PBAM</td>
<td>DCM/H₂O</td>
<td>25</td>
<td>no lactone, SM recovered</td>
</tr>
<tr>
<td>2</td>
<td>NIS</td>
<td>--</td>
<td>PBAM</td>
<td>DCM/H₂O</td>
<td>25</td>
<td>no lactone</td>
</tr>
<tr>
<td>3</td>
<td>NIS</td>
<td>--</td>
<td>PBAM</td>
<td>toluene</td>
<td>25</td>
<td>no lactone</td>
</tr>
<tr>
<td>4</td>
<td>NIS</td>
<td>--</td>
<td>PBAM</td>
<td>toluene</td>
<td>80</td>
<td>no lactone</td>
</tr>
<tr>
<td>5</td>
<td>NIS</td>
<td>--</td>
<td>StilbPBAM</td>
<td>toluene</td>
<td>25</td>
<td>no lactone</td>
</tr>
</tbody>
</table>
7.4. Enantioselective Halolactonizations with Z-Alkenes: Model Studies

Due to the lack of success within these initial saponification-halolactonization attempts, it was determined that the next approach to be taken would be the investigation of a model system. Model studies of a smaller, more accessible substrate would provide insight into the feasibility of achieving halolactonizations with unsaturated carboxylic acids bearing Z-alkenes. Thus, cyclopentenyl cyanocarboxylic acid 576 was seen as an attractive model substrate due to its ease of availability from previously synthesized material. Saponification of ethyl ester 569 with NaOH in aqueous ethanol furnished cyanoacid 576 in good yield (Scheme 194). To our delight, subsequent treatment of acid 576 with NIS and catalytic quantities of DMAP in the presence of DCM delivered the desired iodolactone (577) albeit in modest yield (37%). Acquisition of lactone 577 now set the stage for enantioselective investigations.

**Scheme 194. Racemic Synthesis of Iodolactone 577**

Based on the high degree of success in their respective halolactonization system, reaction conditions described by Dobish and Johnston were used as a template for initial enantioselective studies.245 Herein, PBAM was employed as the chiral organocatalyst, NIS as the iodine source, and toluene (0.05 M) as the solvent. The first variable that was examined was reaction time. When cyanoacid 576 was subjected to the lactonization protocol, iodolactone 577 was afforded in low yield and with minimal levels of enantioselection (12% yield, 5% ee) (Table 29, entry 1). Prolonged reaction times of 12 hours, 24 hours, and 48 hours did not result in any significant change as 577 was acquired in comparable yields and ee’s (Table 29, entries 2-4). Yet when this lactonization was run over the course of 72 hours, lactone 577 was furnished in 4% yield and 17% ee (Table 29, entry 5). Despite this minor improvement in enantioselection, subsequent studies utilized a 24 hour reaction time for the sake of acquiring data in a more timely manner.

The next variable that was probed was solvent concentration. Increasing the concentration from 0.05 M to 0.1 M resulted in higher yield, but minimal loss in enantioselection as iodolactone 577 was furnished in 11% yield and 5% ee (Table 29, entry 6). Further concentrated systems (0.5 M and 1.0 M) confirmed the trends of improved yield and diminished ee (Table 29, entries 7 and
Due to the gradual decrease in enantioselection upon increased solvent concentration, 0.05 M remained as the optimal concentration up to this point.

Table 29. Preliminary Time and Concentration Studies

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>conc. (M)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>0.05</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>0.05</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>0.05</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>0.05</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>0.05</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>0.1</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>0.5</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>1.0</td>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

Introduction of counterions ensued as Brønsted acid salts of BAM ligands led to higher selectivity in previous work. When the triflic acid salt of PBAM (19•HOTf) was used as the catalyst for this system, little change was seen relative to the free base as lactone 577 was afforded in 9% yield and 3% ee (Table 30, entry 2). The triflimide salt of PBAM (19•HNTf₂) performed similarly (Table 30, entry 3). Since acid salts proved ineffective in promoting reactivity and/or selectivity, efforts then shifted towards the use of more Brønsted basic organocatalysts.

Table 30. Effects of Acid Salts and More Brønsted Basic Organocatalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>PBAM•HOTf</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>PBAM•HNTf₂</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>(MeO)PBAM</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>(MeO)PBAM</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>(MeO)₂PBAM</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>---</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

(MeO)PBAM (19d) was employed delivering iodolactonization product 577 in increased yield and diminished ee (11% yield, 1% ee) (Table 30, entry 4). (MeO)PBAM (19e) furnished 577 in
8% yield and 7% ee and $^6,7(\text{MeO})_2\text{PBAM} \ (19c)$ failed to provide product (Table 30, entries 5 and 6). Furthermore, when this lactonization was run in the absence of catalyst, iodolactone 577 was isolated in 7% yield as a racemate (Table 30, entry 7). This indicates that the use of organocatalysts, thus far, have had little or no effect on reactivity and/or selectivity as previously acquired yields are comparable to that of the background reaction.

When the racemic version of this iodolactonization was run, CH$_2$Cl$_2$ was employed as the solvent resulting in the acquisition of lactone 577 in 37% yield (Scheme 194). Since a reasonable yield was observed with CH$_2$Cl$_2$, this solvent was used in the enantioselective variant with ambitions of increasing product formation. Unfortunately, CH$_2$Cl$_2$ performed poorly in the presence of PBAM as lactone 577 was furnished in only 10% yield and 3% ee (Scheme 195). Toluene, therefore, remained as the solvent of choice.

Scheme 195. Iodolactonization Attempt with CH$_2$Cl$_2$ as the Solvent

It should be noted that a 5 mol% loading of PBAM performed similarly relative to when a 10 mol% loading was employed (Table 31, entry 1). Because of these comparable results and for the sake of catalyst economy, 5 mol% catalyst loadings were to be used for subsequent studies.

Table 31. Application of Different Catalyst Backbones and Reevaluation of Temperature and Iodine Sources
Amidine catalysts possessing different backbones were submitted to the halolactonization protocol with the hope of introducing different bite angles that can ultimately promote enantioselection. When StilbPBAM (88) was used as the catalyst, noticeable improvements in yield and selectivity were seen as iodolactone 577 was furnished in 23% yield and 19% ee (Table 31, entry 2). Amidine-amide catalysts in 3,5-(CF₃)₂BenzAM (78a) and PivalAM (78m) performed poorly, however, as loss in yield and/or enantioselection were observed for both of these cases (Table 31, entries 3-4). Encouraged by these results seen with StilbPBAM, lower temperatures were reevaluated in order to see if selectivity could be further improved. When the reaction was chilled to 0 °C and -20 °C respectively, we were delighted to see consistent improvement in ee albeit the gradual depression in yield (Table 31, entries 5 and 6). Unfortunately, running the reaction at -50 °C completely mitigated product formation as no sign of lactone 577 could be detected (Table 31, entry 7). Nevertheless, these improved degrees of enantioselection clearly indicate that the StilbPBAM catalyst is influential in this iodolactonization reaction. Additionally, DIDMH was also reapplied as the iodo source, but still proved inferior relative to NIS (Table 31, entry 8).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>StilbPBAM</td>
<td>toluene</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>StilbPBAM•HOTf</td>
<td>toluene</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>StilbPBAM•HNTf₂</td>
<td>toluene</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>⁶(MeO)StilbPBAM</td>
<td>toluene</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>⁷(MeO)StilbPBAM</td>
<td>toluene</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>⁶(MeO)StilbPBAM</td>
<td>xylenes</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>⁷(MeO)StilbPBAM</td>
<td>THF</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>⁶(MeO)StilbPBAM</td>
<td>CHCl₃</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Acid salts were employed once more with the ambition of further enhancing selectivity. Unfortunately, both the triflic acid and triflimide salts of StilbPBAM (88•HOTf and 88•HNTf₂) gave lower yield and diminished enantioselection reaffirming the superiority of the free base catalyst (Table 32, entries 2 and 3). These results led to the examination of more Brønsted basic stilbene diamine-derived ligands. When ⁶(MeO)StilbPBAM (88a) was employed as the organocatalyst, mild improvement was observed as lactone 577 was furnished in 24% yield and...
32% ee (Table 32, entry 4). $^7$(MeO)StilbPBAM (88b) did not fare as well as 577 was acquired in only 11% yield and 26% ee (Table 32, entry 5).

With $^6$(MeO)StilbPBAM (88b) chosen as the new optimal catalyst, the effects of different solvents were examined more extensively. Interestingly, xylenes, a solvent similar to that of toluene, failed to yield any product when subjected to the halolactonization protocol (Table 32, entry 6). The same was observed with an ethereal solvent in THF (Table 32, entry 7). CH$_3$CN was also used, but proved inferior relative to toluene as lactone 577 was afforded in only 4% yield and 3% ee (Table 32, entry 8). Once again, toluene remained the solvent of choice.

Non-BAM catalysts were submitted next in order to see their respective influence on product yield and enantioselection. 2,4,6-Triisopropyl-phenyl-based binaphthol phosphoric acid (TRIP) catalyst 578 was ineffective as no product was furnished upon its use (Table 33, entry 2). Deng’s and Takemoto’s thiourea organocatalysts (579 and 68) were also employed, but to no avail as lactone 577 was isolated in minimal yield and as a racemate in both cases (Table 33, entries 3 and 4).

### Table 33. Studies with Non-BAM Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$^6$(MeO)StilbPBAM</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>TRIP</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Deng Thiourea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Takemoto Thiourea</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>


At this point, every variable within this reaction system has been examined to an extent with the optimal result being a 24% isolated yield of lactone 577 with 32% ee. Since modification of these variables did not provide good yields and promising levels of enantioselection, efforts then shifted towards the use of other electrophilic halogen sources (i.e. bromine and chlorine). With aspirations of achieving bromolactonization, cyanoacid 576 was treated with N-bromosuccinimide (NBS) and DMAP in the presence of CH₂Cl₂. Gratifyingly, the desired bromolactone 580 was successfully acquired albeit in 19% yield (Scheme 196).

**Scheme 196. Racemic Synthesis of Bromolactone 580**

Investigation of the enantioselective variant of this bromolactonization commenced when acid 576 was treated with PBAM (5 mol%) and NBS in the presence of toluene at -20 °C. After a 24 hour reaction period, no sign of bromolactone 580 could be detected (Table 34, entry 1). The same result was seen when StilbPBAM was employed as the catalyst (Table 34, entry 2). The use of a different bromine source in N-bromophthalimide (NBP) also proved fruitless as this too failed to provide product (Table 34, entry 3).

**Table 34. Brief Investigation of an Enantioselective Bromolactonization**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>bromine source</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>NBS</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>StilbPBAM</td>
<td>NBS</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>StilbPBAM</td>
<td>NBP</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Due to the limitations of this bromolactonization reaction, efforts shifted towards the development of a chlorolactonization system. This approach was even more problematic as treatment of cyanoacid 576 with N-chlorosuccinimide (NCS) and DMAP in the presence of CH₂Cl₂ failed to deliver racemic chlorolactone 581 (Scheme 197). Since chlorolactone 581 could not be isolated as a racemate, no analytical assay could be developed ultimately preventing enantioselective studies.
Selenolactonization with acid 576 was the next avenue that was explored. Subjection of acid 576 to N-(phenylseleno)phthalimide (PSP) and DMAP in the presence of CH$_2$Cl$_2$ provided selenolactone 582 in 21% yield as a racemate (Scheme 198). Acquisition of this selenolactone set the stage for the enantioselective variation of this reaction system.

Enantioselective investigations began when cyanoacid 576 was treated with PBAM (5 mol%) and PSP in the presence of toluene at room temperature. After 24 hours, no promising levels of enantioselection were observed as selenolactone 582 was furnished in 26% yield and 2% ee (Table 35, entry 1). Replacing PBAM with StilbPBAM did not show any improvement as a racemic mixture of 582 was delivered in 23% yield (Table 35, entry 2). Both PBAM and StilbPBAM were reemployed in the selenolactonization protocol at -20 °C. Chilled temperatures did not show improvement as selenolactone 582 was isolated but as a racemate in 18% and 21% yields, respectively (Table 35, entries 3 and 4). Furthermore, the triflic acid and triflimide salts of StilbPBAM also proved ineffective as no improvement in yield and/or ee were observed (Table 35, entries 5 and 6).

**Table 35. Brief Investigation of an Enantioselective Selenolactonization**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>T (°C)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>25</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>StilbPBAM</td>
<td>25</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PBAM</td>
<td>-20</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>StilbPBAM</td>
<td>-20</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>StilbPBAM•HOTf</td>
<td>-20</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>StilbPBAM•HNTf</td>
<td>-20</td>
<td>23</td>
<td>0</td>
</tr>
</tbody>
</table>
The focus then centered upon the development of a 6-membered model system as multiple variations of the 5-membered system showed little or no promise. The substrate of choice for these 6-membered model studies was that of cyanoacid 583, the homologated analog of cyanoacid 576. Thus, compound 583 could be readily accessed upon subjecting acid 576 to an Arndt-Eistert homologation process. Treatment of 576 with SOCl₂ provided acid chloride 584 (Scheme 199). Subsequent exposure of this acyl chloride to diazomethane in diethyl ether furnished diazoketone 585 in modest yield (38% over 2 steps). 585 then underwent homologation when treated with silver benzoate (AgOBz) under basic conditions ultimately delivering methyl ester 586 in 64% yield. Saponification of ester 586 with hydroxide in aqueous methanol afforded the desired precursor acid 583 (88% yield). Acid 583 was successfully converted to [6.5]-bicyclic iodolactone 587 in moderate yield when treated with NIS and DMAP in the presence of CH₂Cl₂ (37%).

Investigation of the enantioselective version of this 6-membered iodolactonization began when acid 583 was treated with PBAM (5 mol%) and NIS in toluene at room temperature. Lactone 587 was acquired in 12% yield and 4% ee after a 24 hour reaction time (Table 36, entry 1). StilbPBAM showed no improvement as lactone 587 was obtained in 14% yield as a racemate (Table 36, entry 2). Triflic acid and triflimide salts of StilbPBAM also proved fruitless as yields and enantioselection remained relatively unchanged (Table 36, entries 3 and 4).

Various solvents were examined next in order to see their respective influence on this lactonization protocol. CH₂Cl₂ resulted in an improvement in yield as lactone 587 was furnished in 25% yield (Table 36, entry 5). However, the enantiopurity was similar to that observed with toluene (3% ee). Nitromethane (MeNO₂) did not show any enhancement as iodolactone 587 was delivered in 19% yield as a racemate (Table 36, entry 6). Alcoholic (MeOH) and nitrile (CH₃CH₂CN) solvents performed similarly to that of MeNO₂, and THF failed to give product.

Scheme 199. Racemic Synthesis of [6.5]-Bicyclic Iodolactone 587

![Chemical diagram](image)

Investigation of the enantioselective version of this 6-membered iodolactonization began when acid 583 was treated with PBAM (5 mol%) and NIS in toluene at room temperature. Lactone 587 was acquired in 12% yield and 4% ee after a 24 hour reaction time (Table 36, entry 1). StilbPBAM showed no improvement as lactone 587 was obtained in 14% yield as a racemate (Table 36, entry 2). Triflic acid and triflimide salts of StilbPBAM also proved fruitless as yields and enantioselection remained relatively unchanged (Table 36, entries 3 and 4).

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completely (Table 36, entries 7-9). Although CH$_2$Cl$_2$ led to improved yield, toluene was taken onto further studies as noticeable levels of enantioselection were achieved with this solvent in the 5-membered lactonization system.

**Table 36. 6-Membered Iodolactonization: Catalyst and Solvent Studies**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>toluene</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>StilbPBAM</td>
<td>toluene</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>StilbPBAM•HOTf</td>
<td>toluene</td>
<td>17</td>
<td>-5</td>
</tr>
<tr>
<td>4</td>
<td>StilbPBAM•HNTf$_2$</td>
<td>toluene</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>PBAM</td>
<td>CH$_2$Cl$_2$</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>PBAM</td>
<td>MeNO$_2$</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PBAM</td>
<td>MeOH</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>PBAM</td>
<td>CH$_2$CH$_2$CN</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>PBAM</td>
<td>THF</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Other non-amidine organocatalysts were also employed with aspirations of increasing yield and selectivity. When 3,5-(bistrifluoromethyl)phenyl-based binaphthol (BINOL) 588 was used as the catalyst, little change was seen relative to PBAM as lactone 587 was isolated in 14% yield and 3% ee (Table 37, entry 2). BINOL phosphoric acid 589 and phenanthrene-derived BINOL phosphoric acid 590 performed similarly (Table 37, entries 3 and 4). Anthracene-derived BINOL phosphoric acid catalyst 591 showed mild improvement as the iodolactone product was isolated in 17% yield and 8% ee (Table 37, entry 5). 2,6-Dimethyl-4-methoxy-phenyl-based BINOL phosphoric acid 592 did not fare as well as this catalyst delivered lactone 587 in 7% yield as a racemate (Table 37, entry 6). TRIP as well as Deng’s and Takemoto’s thioureas also proved

**Figure 36. Potential Unwanted Electronic Interaction in the Binding Mode**
ineffective as diminished yields and selectivities were observed relative to when PBAM was used (Table 37, entries 7-9).

**Table 37.** 6-Membered Iodolactonization: Examination of Non-Amidine Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>BINOL 588</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>phosphoric acid 589</td>
<td>17</td>
<td>-5</td>
</tr>
<tr>
<td>4</td>
<td>phosphoric acid 590</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>phosphoric acid 591</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>phosphoric acid 592</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>TRIP</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Deng Thiourea</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Takemoto Thiourea</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

The inability to achieve promising levels of enantioselection with a multitude of Z-alkene substrates resulted in the analysis of potential problems. One commonality between the starting materials employed throughout the course of these lactonization studies is that they all possess a cyano motif. Also, the fact that 32% ee was observed within the 5-membered iodolactonization system suggests that the starting cyanoacid is indeed binding to the organocatalyst (Table 32, entry 4). With these observations in mind, it is reasonable to infer that the cyano group of the acid may be involved in an unwanted electronic interaction when binding to the organocatalyst (Figure 36). In other words, the cyano motif may be preventing the acid from orienting itself with the catalyst in such a way that favors higher levels of enantioselection. In order to neutralize this potential problem, the cyano functionality should be replaced with a moiety less prone to undesired electronic interaction (i.e. a phenyl group). Therefore, phenyl cyclopentene carboxylic acid 593 was the next substrate of interest.
Acid 593 was synthesized via a known procedure as described by Takacs and colleagues. Treatment of commercially available methyl phenylacetate (594) with NaH and cis-1,4-dichloro-2-butene in the presence of N,N'-dimethylpropylene urea (DMPU) and THF at elevated temperature provided methyl phenylcyclopentene carboxylate 595 in 42% isolated yield (Scheme 200). Subsequent saponification of 595 with KOH in ethanol furnished known acid 593 in 95% yield. When this acid was treated with NIS and DMAP in CH₂Cl₂, iodolactone 596 was afforded setting the stage for enantioselective studies.

Scheme 200. Racemic Synthesis of Iodolactone 596

With a phenyl motif in place of the cyano group, we were hopeful that acid 593 would achieve a binding mode that would ultimately increase selectivity. When PBAM was used as the organocatalyst, we were disappointed to see that this substrate was not immediately better behaved as lactone 596 was acquired in 9% yield and 1% ee (Table 38, entry 1). However, when StilbPBAM was employed, increased yield and promising levels of enantioselection were observed as the lactone product was isolated in 25% yield and 48% ee (Table 38, entry 2). This jump in selectivity between the PBAM and StilbPBAM entries indicates that the bite angle of the catalyst is critical for inducing high levels of enantioselection. Encouraged by the StilbPBAM result, the triflic acid and triflimide salts of StilbPBAM were also submitted with aspirations of further enhancing enantioselection. Unfortunately, neither of these fared as well relative to the free base catalyst (Table 38, entries 3 and 4).

With StilbPBAM taken on as the catalyst, the effects of temperature were examined next. Subjection of StilbPBAM to the reaction protocol at 0 °C led to an increase in both yield and enantioselection as lactone 596 was afforded in 41% yield and 58% ee (Table 38, entry 5). A -20 °C reaction temperature provided the lactone product in 30% yield and 65% ee confirming that

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lower temperatures correlate to higher ee (Table 38, entry 6). However, when the lactonization was further chilled to -50 °C and -78 °C, product formation was completely mitigated (Table 38, entries 7 and 8).

After identifying -20 °C as the optimum temperature, organocatalysts with higher Brønsted basicity profiles were studied next. When 7(MeO)StilbPBAM was employed as the catalyst, we were disappointed to see a dramatic drop in yield and selectivity as lactone 596 was provided in only 11% yield and 12% ee (Table 38, entry 9). An anthracenyl-bearing analog, dubbed 7(MeO)AnthPBAM (597), was also examined in the iodolactonization system. Unfortunately, this catalyst also proved fruitless as lactone 596 was delivered in 10% yield and -3% ee (Table 38, entry 10).

### Table 38. Initial Iodolactonization Studies with Phenyl-Derived Acid 593

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp. (°C)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBAM</td>
<td>25</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>StilbPBAM</td>
<td>25</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>StilbPBAM•HOTf</td>
<td>25</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>StilbPBAM•HNTf</td>
<td>25</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>StilbPBAM</td>
<td>0</td>
<td>41</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>StilbPBAM</td>
<td>-20</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>StilbPBAM</td>
<td>-50</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>StilbPBAM</td>
<td>-78</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>7(MeO)StilbPBAM</td>
<td>-20</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>7(MeO)AnthPBAM</td>
<td>-20</td>
<td>10</td>
<td>-3</td>
</tr>
</tbody>
</table>

With promising levels of enantioselection achieved, other variables are to be examined in order to further improve this system. These variables include different iodine sources, solvents, and other catalysts modifications. These efforts are currently ongoing within our laboratory by Matthew Knowe and Zachary Carter.

### 7.5. Future Directions

The immediate objectives are to improve the yield of this iodolactonization and to achieve levels of enantioselection that are high enough for synthetic utility (i.e. >90% ee). The most direct avenues of accomplishing these goals include examining the effects of catalysts modifications as well as different iodine sources and solvents. Additionally, substrates with different steric and
electronic properties can be employed in order to see their respective influence on this reaction system. Once this iodolactonization is achieved in sufficient yield and optimal levels of enantioselection, this protocol can be applied to a multitude of Z-alkene bearing carboxylic acids in order to demonstrate the generality of this methodology (Scheme 201).

**Scheme 201. Reaction Optimization and Substrate Scope Development**

Another future direction would be to apply this newly developed methodology towards the synthesis of sesbanine (531). Pyridyl cyclopentene carboxylic acid 598 can be synthesized as a precursor substrate to the iodolactonization protocol. Subjection of acid 598 to optimal reaction conditions can theoretically deliver iodolactone 599 in good yield and with high levels of enantioselection. This lactone intermediate can then be converted to sesbanine (531) via a short synthetic sequence (Scheme 202).

**Scheme 202. Revised Proposed Synthesis of Sesbanine**
Chapter 8. Experimentals

Glassware was flame-dried under vacuum for all non-aqueous reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), and toluene was dried by passage through a column of activated alumina as described by Grubbs.$^{252}$ This was done to accurately quantitate the amount of water in each reaction.

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 µm) plates and flash chromatography utilized 230-400 mesh silica gel from Sorbent Technologies. UV light and/or the use of potassium permanganate solutions were used to visualize products.

IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm$^{-1}$). All compounds were analyzed as neat films on a NaCl plate (transmission). Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 for CDCl$_3$. Mass spectra were recorded on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of electron impact ionization (EI) or electrospray ionization (ESI) by the Indiana University Mass Spectrometry Facility. Optical rotations were measured on a Perkin Elmer-341 polarimeter. Chiral HPLC analysis was conducted on an Agilent 1100 series instrument using the designated ChiralPak column.

2,4-Dichloro-$N$-((1-((1-methyl-1H-imidazol-4-yl) sulfonyl)azetidin-3-yl)(phenyl) methyl) benzamide (1). To a flame dried flask equipped with a stir bar was added the amine (36.1 mg, 118 µmol) and dichloromethane (1 mL), immediately followed by addition of $N$,$N$-

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diisopropylethylamine (30.5 mg, 236 µmol) and the benzoyl chloride (42.1 mg, 201 µmol). The reaction was stirred at rt for 16 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with NaHCO$_3$, extracted with dichloromethane, dried (MgSO$_4$), filtered and concentrated in vacuo. Flash column chromatography of the residue (SiO$_2$, 0-10% methanol in dichloromethane) yielded the desired dichlorinated product as an off white viscous oil (15.3 mg, 27% over 2 steps). The major enantiomer was determined to be 87% ee by chiral HPLC analysis. Chiral HPLC analysis (Chiralpak AD, 65% isopropyl alcohol/hexanes, 1.2 mL/min, $t_r(e_1, \text{major}) = 3.65$ min, $t_r(e_2, \text{minor}) = 7.05$ min); $[\alpha]_{D}^{20} = -4.6$ (c 0.41, CHCl$_3$); R$_f$ = 0.40 (5% MeOH/dichloromethane); IR (film) 3262, 3061, 2925, 2855, 1649 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52 (s, 1H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.40 (d, $J = 2.0$ Hz, 1H), 7.38 (s, 1H), 7.31 (m, 4H), 7.22 (d, $J = 6.8$ Hz, 2H), 6.83 (br d, $J = 8.4$ Hz, 1H), 5.06 (dd, $J = 8.8, 8.8$ Hz, 1H), 4.07 (dd, $J = 8.4, 8.4$ Hz, 1H), 3.96 (dd, $J = 8.4, 8.4$ Hz, 1H), 3.95 (d, $J = 7.2$ Hz, 2H), 3.79 (s, 3H), 3.03 (ddddd, $J = 8.8, 8.4, 7.2, 7.2$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 165.3, 138.6, 136.9, 133.4, 131.5, 131.0, 129.9, 129.0, 128.2, 127.5, 126.5, 55.5, 54.0, 53.6, 34.2, 33.3; HRMS (ESI): Exact mass calcd for C$_{21}$H$_{21}$Cl$_2$N$_4$O$_3$S [M+H]$^+$ 479.0679, found 479.0714. HSQC indicated that the methylene carbons of the azetidine ring are diastereotopic, as would be expected for the assigned structure.

**Summary of Structural Elucidation for Azetidine 1.**

**Key Features**

The structure was assigned as the desired azetidine using standard 1D and 2D NMR techniques. $^1$H NMR indicated the presence of a doublet of doublets integrating to 1H at 4.07 ppm, a doublet of doublets integrating to 1H at 3.96 ppm and a doublet integrating to 2H at 3.95. These 4 hydrogens account for both methylenes of the azetidine ring. The unorthodox splitting of the azetidine methylenes supported the proposal that the hydrogens on the methylenes of the azetidine ring were diasterotopic (all magnetically inequivalent). $^1$H NMR also indicated the presence of a doublet of doublets integrating to 1H at 5.06 ppm, assigned as the benzylic methine. A singlet integrating to 3H at 3.79 ppm was assigned as the methyl group of the methyl imidazole ring. A doublet of doublets of doublets of doublets integrating to 1H at 3.03 ppm was assigned as the methine of the azetidine ring. Also, the presence of 10H in the aromatic region further supports the desired azetidine structure. $^{13}$C NMR clearly indicates the presence of an amide at 165 ppm. Peaks at 54.0 ppm and 53.6 ppm indicates that the methylene carbons of the azetidine
ring are diastereotopic. DEPT 135 experimentation further confirms this finding as the peaks at 54.0 ppm and 53.6 ppm are inverted indicating that they are methylene carbons.

Additional Features

Key HSQC Correlations for 1 (600 MHz)

![Chemical Structure]

Further evidence supporting the structural assignment includes an HSQC, which clearly showed that the methylene hydrogens and carbons on the azetidine ring were diastereotopic via anticipated $^1J_{HC}$ couplings. C1 (54.0 ppm) of the azetidine ring showed correlations to methylene hydrogens H3 (4.07 ppm) and H4 (3.95 ppm). C2 (53.6 ppm) of the azetidine ring also showed correlations to methylene hydrogens H5 (3.96 ppm) and H4' (3.95 ppm).

Benzyl 3-(((tert-butoxycarbonyl)amino)(phenyl)methyl)azetidine-1-carboxylate (21). To a solution of the nitro azetidine (75.0 mg, 170 µmol) in toluene (2.1 mL) at room temperature was added $^\circ$Bu$_3$SnH (99.0 mg, 340 µmol). The resulting mixture was heated to 110 °C, immediately followed by the addition of azobisisobutyronitrile (AIBN) (6.00 mg, 34.0 µmol). After the reaction mixture stirred for 1 h at 110 °C, additional AIBN (6.00 mg, 34.0 µmol) was added and the mixture was stirred at 110 °C for an additional 3 h. The reaction was cooled, concentrated, diluted with diethyl ether and washed with satd aq KF. The organic layer was dried (MgSO$_4$), filtered through a Celite pad with additional diethyl ether and concentrated. Flash column chromatography of the residue (SiO$_2$, 20-30% ethyl acetate in hexanes) yielded the desired azetidine as a white solid (45.0 mg, 67%). $[α]^{20}_D$ -26.7 (c 0.69, CHCl$_3$); mp 110-112 °C; R$_f$ = 0.20 (25% EtOAc/hexanes); IR (film) 3328, 3032, 2973, 2886, 1705 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 (m, 8H), 7.21 (d, J
= 7.2 Hz, 2H), 5.09 (s, 2H), 4.89 (br s, 1H), 4.82 (br s, 1H), 4.10 (dd, \(J = 8.4, 8.4\) Hz, 1H), 3.98 (br dd, \(J = 5.6, 5.6\) Hz, 1H), 3.91 (br dd, \(J = 8.8, 8.8\) Hz, 1H), 3.69 (br dd, \(J = 6.0, 6.0\) Hz, 1H), 2.94 (br s, 1H), 1.41 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 156.3, 155.4, 140.1, 136.5, 128.7, 128.3, 127.9, 127.8, 127.7, 126.5, 79.7, 66.5, 56.8, 51.6, 51.1, 34.1, 28.2; HRMS (ESI): Exact mass calcd for C\(_{23}\)H\(_{28}\)N\(_2\)NaO\(_4\) [M+Na\(^+\)] 419.1898, found 419.1927.

**Benzyl 3-(amino(phenyl)methyl)azetidine-1-carboxylate (22).** To a flame dried flask equipped with a stir bar was added the carbamate (90.0 mg, 227 \(\mu\)mol) and 4 M HCl·dioxane (426 \(\mu\)L, 1.71 mmol). The resulting mixture was allowed to stir at rt for 16 h prior to TLC analysis. Concentration of the reaction mixture yielded the chloride salt of the desired amine as a light yellow foam. The unpurified material was used in the next step.

**Benzyl 3-((2,4-dichlorobenzamido)(phenyl)methyl)azetidine-1-carboxylate (24).** To a flame dried flask equipped with a stir bar was added the chloride salt of the amine (76.0 mg, 228 \(\mu\)mol) and dichloromethane (2 mL). The resulting solution was chilled to 0 \(^\circ\)C, immediately followed by addition of \(N,N\)-diisopropylethylamine (70.7 mg, 547 \(\mu\)mol) and the benzoyl chloride (71.8 mg, 343 \(\mu\)mol). The mixture was warmed to room temperature, stirred for 16 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with NaHCO\(_3\), extracted with dichloromethane, dried (MgSO\(_4\)), filtered and concentrated. Flash column chromatography of the residue (SiO\(_2\), 10-40% ethyl acetate in hexanes) yielded the desired amide as an off white oil (44.4 mg, 42% over 2 steps). \([\alpha]_{D}^{20}\) -13.4 (c 0.90, CHCl\(_3\)); \(R_f = 0.41\) (40% EtOAc/hexanes); IR (film) 3264, 3064, 2925, 2854, 1710, 1643 cm\(^{-1}\), \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64 (d, \(J = 8.4\) Hz, 1H), 7.44 (br d, \(J = 1.2\) Hz, 1H), 7.35 (m, 11H), 7.17 (br d, \(J = 8.4\) Hz, 1H), 5.57 (br t, \(J = 8.0, 8.0\) Hz, 1H), 5.41 (br s, 1H), 5.11 (s, 1H), 3.66 (dd, \(J = 11.6, 3.6\) Hz, 1H), 3.57
Methyl ((2S)-1-(2,4-dichlorobenzoyl) -2-phenylazetidin-3-yl) methyl carbamate (26). To a flame dried flask equipped with a stir bar was added the benzamide (37.0 mg, 79.0 µmol), methanol (2 mL) and 40% KOH (301 µL, 3.15 mmol). The reaction mixture was heated to 45 °C, allowed to stir for 16 h, and then concentrated. The resulting residue was diluted with water, extracted with dichloromethane and the organic extracts were dried (MgSO₄), filtered and concentrated. Flash column chromatography of the crude material (SiO₂, 10-50% ethyl acetate in hexanes) yielded the desired methyl ester as an off white viscous oil (12.4 mg, 40%). [α]D²⁰ +24.5 (c 1.24, CHCl₃); Rf = 0.24 (40% EtOAc/hexanes); IR (film) 3327, 3062, 3029, 2927, 2361, 1716, 1663 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.55 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.37 (dd, J = 7.8, 7.8 Hz, 2H), 7.28 (m, 4H), 4.82 (br s, 1H), 4.54 (d, J = 6.0 Hz, 1H), 4.31 (dd, J = 11.4, 3.6 Hz, 1H), 4.16 (dd, J = 10.8, 6.6 Hz, 1H), 3.67 (s, 3H), 3.33 (m, 2H), 2.22 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃) ppm 157.3, 155.7, 142.2, 136.0, 133.3, 132.5, 131.3, 130.0, 128.6, 127.4, 127.2, 127.0, 65.1, 58.9, 52.3, 41.0, 39.2; HRMS (ESI): Exact mass calcd for C₁₉H₁₉Cl₂N₂O₃ [M+H]⁺ 393.0779, found 393.0766. HMBC (600 MHz) analysis further confirmed the compound structure.

**Structural Elucidation for Methyl Ester 26**

**Key Features**

The structure was assigned as the methyl ester using standard 1D and 2D NMR techniques. ¹H NMR indicated the presence of a singlet integrating to 3H at 3.67 ppm, assigned as the CH₃O-fragment. The presence of a multiplet integrating to 2H at 3.33 ppm indicates the presence of a methylene group alpha to the nitrogen of the carbamate. The presence of this methylene group also
supports the proposal of an azetidine isomerization. The absence of the benzyl peak at 5.1 ppm supports that the Cbz was successfully cleaved. Also, the presence of approximately 8H in the aromatic region is consistent with the cleavage of the Cbz group. $^{13}$C NMR clearly indicates the presence of a carbamate at 157.3 ppm and an amide at 155.7 ppm. DEPT 135 experimentation shows the presence of two methylenes, one cyclic at 65.1 ppm, and one acyclic at 41.0 ppm. The presence of these two methylenes with such a large difference in chemical shift further supports the assignment based on azetidine isomerization.

Additional Features

Key HMBC Correlations for Methy Ester 26 (600 MHz)

Further evidence supporting the structural assignment includes an HMBC, which clearly showed the anticipated $^3J_{HC}$ couplings for desired methyl ester 26. C1 (157 ppm) of the carbamate showed correlations to H2/H2'/H2'' (3.67 ppm) and H3/H3'(3.33 ppm). C4 (156 ppm) of the amide showed correlations to diastereotopic methylene hydrogens H5 (4.31 ppm) and H6 (4.16 ppm) as well as to H7 (7.55 ppm) and methine hydrogen H8 (4.54 ppm). Furthermore, methylene C9 (41.0 ppm) showed correlations to diastereotopic methylene hydrogens H5 (4.31 ppm) and H6 (4.16 ppm) and to methine hydrogen H8 (4.54 ppm).

Benzyl ((2S)-1-(2,4-dichlorobenzoyl)-2-phenylazetidin-3-yl)methyl)carbamate (27). To a flame dried flask equipped with a stir bar was added the benzamide (37.0 mg, 79.0 µmol), methanol (2 mL) and 40% KOH (301 µL, 3.15 mmol). The reaction mixture was heated to 45 °C,
allowed to stir for 16 h then concentrated in vacuo. The resulting residue was diluted with water, extracted with dichloromethane and the organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. Flash column chromatography of the crude material (SiO₂, 10-50% ethyl acetate in hexanes) yielded the desired azetidine as a light yellow oil (5.8 mg, 16%). \[ \alpha \]D²⁰ +13.9 (c 1.24, CHCl₃); \( R_f \) = 0.37 (40% EtOAc/hexanes); IR (film) 3328, 3031, 2924, 2853, 1713, 1664 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.54 (d, \( J = 8.4 \) Hz, 1H), 7.43 (d, \( J = 2.0 \) Hz, 1H), 7.35 (m, 8H), 7.28 (m, 3H), 5.10 (m, 2H), 4.88 (br s, 1H), 4.54 (d, \( J = 5.6 \) Hz, 1H), 4.31 (dd, \( J = 11.2, 3.2 \) Hz, 1H), 4.16 (dd, \( J = 11.2, 6.8 \) Hz, 1H), 3.35 (dd, \( J = 10.0, 6.0 \) Hz, 2H), 2.24 (br d, \( J = 3.2 \) Hz, 1H); \(^13\)C NMR (150 MHz, CDCl₃) ppm 156.6, 155.8, 142.2, 136.3, 136.0, 133.3, 132.5, 131.3, 130.0, 128.7, 128.6, 128.3, 128.1, 127.4, 127.2, 127.0, 67.0, 65.0, 58.7, 41.1, 39.1; HRMS (ESI): Exact mass calcd for C₂₅H₂₃Cl₂N₂O₃ [M+H]⁺ 469.1079, found 469.1098. HMBC (600 MHz) analysis further confirmed the compound structure.

**Structural Elucidation for Azetidine Isomer 27**

**Key Features**

The structure was assigned as the azetidine isomer using standard 1D and 2D NMR techniques. \(^1\)H NMR indicated the presence of a doublet integrating to 2H at 5.10 ppm, assigned as the benzyl methylene of the Cbz protecting group. The presence of a multiplet integrating to 2H at 3.35 ppm indicates the presence of a methylene group alpha to the nitrogen of the carbamate. The presence of this methylene group also supports the proposal of the azetidine isomerization. Also, the presence of approximately 13H in the aromatic region further supports that the Cbz group remained intact. \(^13\)C NMR clearly indicates the presence of a carbamate at 156.6 ppm and an amide at 155.8 ppm. DEPT 135 experimentation shows the presence of three methylenes, one cyclic at 65.0 ppm, and two acyclic at 67.0 ppm and 41.1 ppm. The methylene at 67.0 ppm is indicative of the benzyl carbon of the Cbz. The presence of the two methylenes with such a large difference in chemical shift (65.0 ppm and 41.1 ppm) further supports the idea that azetidine isomerization did occur.
Additional Features

**Key HMBC Correlations for Azetidine Isomer 27 (600 MHz)**

Further evidence supporting the structural assignment includes an HMBC, which clearly showed the anticipated $^3J_{HC}$ couplings for desired isomer 27. C1 (157 ppm) of the carbamate showed correlations to $\text{H3/H3}'$ (3.35 ppm) and $\text{H2/H2}'$ (5.10 ppm). C4 (156 ppm) of the amide showed correlations to diastereotopic methylene hydrogens H5 (4.31 ppm) and H6 (4.16 ppm) as well as to H7 (7.54 ppm) and methine hydrogen H8 (4.54 ppm). Furthermore, methylene C9 (41.1 ppm) showed correlations to diastereotopic methylene hydrogen H5 (4.31 ppm) and to methine hydrogen H8 (4.54 ppm).

**tert-Butyl (azetidin-3-yl(phenyl)methyl)carbamate (28).** To a flame dried flask equipped with a stir bar was added the carbamate (50.0 mg, 126 µmol) followed by the addition of 5% Pd/C (27.0 mg, 130 µmol). Methanol (1 mL) was then added and the resulting suspension was allowed to stir for 5 minutes. The flask and its contents were purged with H$_2$ gas and left to stir under H$_2$ atmosphere (balloon) at rt for 3 h. The reaction mixture was filtered through a Celite pad with methanol and dichloromethane and then concentrated in vacuo to afford the desired amine as a colorless oil. The unpurified material was used in the next step.
**tert-Butyl((1-(1-methyl-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)(phenyl)methyl carbamate (30).** To a flame dried flask equipped with a stir bar was added the azetidine (33.0 mg, 126 µmol) and dichloromethane (3 mL), immediately followed by addition of the sulfonyl chloride (27.0 mg, 151 µmol) and N,N-diisopropylethylamine (19.5 mg, 151 µmol). The reaction was stirred at rt for 16 h, diluted with water and extracted with ethyl acetate. The organic extracts were then washed with brine, dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 0-10% methanol in dichloromethane) yielded the sulfonamide as an off white viscous oil (28.7 mg, 56% over 2 steps). \([\alpha]^{20}_D -12.5 (c 0.77, \text{CHCl}_3); R_f = 0.4 (5\% \text{ MeOH/dichloromethane});\]

**IR (film) 3368, 3134, 2977, 1703, 1526 cm⁻¹;**

**¹H NMR (400 MHz, CDCl₃) δ 7.62 (s, 1H), 7.51 (s, 1H), 7.25 (m, 3H), 7.12 (d, \(J = 7.2\) Hz, 2H), 5.21 (br d, \(J = 5.2\) Hz, 1H), 4.48 (dd, \(J = 8.8, 8.8\) Hz, 1H), 3.97 (dd, \(J = 8.4, 8.4\) Hz, 1H), 3.85 (dd, \(J = 8.4, 8.4\) Hz, 1H), 3.84 (d, \(J = 8.0\) Hz, 2H), 3.79 (s, 3H), 2.84 (dddd, \(J = 8.8, 8.4, 8.4, 8.0, 8.0\) Hz, 1H), 1.38 (s, 9H);**

**¹³C NMR (100 MHz, CDCl₃) ppm 155.3, 139.8, 139.6, 136.2, 128.7, 127.7, 126.2, 125.9, 79.6, 56.3, 53.9, 53.5, 34.1, 33.6, 28.2;**


**(1-(1-Methyl-1H-imidazol-4-yl)sulfonyl)azetidin-3-yl)(phenyl)methanamine (31).** To a flame dried flask equipped with a stir bar was added the sulfonamide (48.0 mg, 118 µmol) and 4 M HCl·dioxane (220 µL, 886 µmol). The resulting mixture was allowed to stir at rt for 16 h before it was diluted with dichloromethane and washed with NaHCO₃. The organic layer was then separated, dried (MgSO₄), filtered, and concentrated to afford the desired amine as a cloudy oil. The unpurified material was used in the next step.
General procedure for (1S,(S,S))-N-(p-Tolylsulfinyl)-2-nitro-1-phenyl-1-methyl-ethanamine (54a) and (1R,(S,S))-N-(p-Tolylsulfinyl)-2-nitro-1-phenyl-1-methyl-ethanamine (54b). This procedure was modified off of a previous protocol found in literature.\textsuperscript{27} To a flame-dried vial equipped with a stirbar was added the ketimine (31.7 mg, 123 \( \mu \)mol) and nitromethane (1.00 mL, 18.6 mmol). Tetra-\( n \)-butylammonium fluoride (6.43 mg, 24.6 \( \mu \)mol) was then added and the mixture was allowed to stir at rt for 18 h. The reaction mixture was filtered through a silica pad with dichloromethane and ethyl acetate and concentrated in vacuo. Flash column chromatography of the residue (SiO\(_2\), 10-40\% ethyl acetate in hexanes) yielded the desired adduct as a colorless oil (23.2 mg, 59\%). For characterization data of this compound, refer to the supporting information of the literature reference cited in this experimental.

General Procedure for (S)-4-Methyl-N-(1-nitro-2-phenylpropan-2-yl)benzenesulfonamide (58). To a vial equipped with a stir bar was added the ketimine (15.0 mg, 54.9 \( \mu \)mol), PBAM (5.60 mg, 11.0 \( \mu \)mol), and dichloroethane (440 \( \mu \)L). Once the mixture was homogenous, nitromethane (5.90 \( \mu \)L, 110 \( \mu \)mol) was added in one portion and the reaction mixture stirred for 96 h. The reaction mixture was filtered through a silica pad with dichloromethane and ethyl acetate and was then concentrated in vacuo. Flash column chromatography of the residue (SiO\(_2\), 15-20\% ethyl acetate in hexanes) yielded the desired adduct as a white amorphous solid (2.4 mg, 13\%). The characterization data for this compound was found in the literature.\textsuperscript{28}
(E)-4-Nitro-N-(1-phenylethylidene)benzenesulfonamide (59). This procedure was modified off of protocols found in literature.32,253 To an oven dried 2-necked round bottom flask equipped with a condesor and a stir bar was added the sulfonamide (937 mg, 4.63 mmol), acetophenone (1.11g, 9.27 mmol), ZnCl₂ (156 mg, 927 µmol), and Ti(OEt)₄ (5.29 mg, 23.2 mmol). The resulting mixture stirred under vacuum for 15 minutes. Toluene (24.0 mL) was then added and the solution was heated to reflux for 72 h. The solution was then cooled to 0 °C followed by the addition of MeOH (15 mL), DCM (15 mL), and sat aq NaHCO₃ (13 mL). The resulting solid was filtered and washed with dichloromethane. Organic extracts were dried (MgSO₄), filtered, and concentrated. Flash column chromatography of the residue (SiO₂, 3%-50% ethyl acetate in hexanes) afforded the desired ketimine as a yellow to orange solid (93 mg, 7%). The characterization data for this compound was found in the literature.254

(E)-4-Methoxy-N-(1-phenylethylidene)benzenesulfonamide (60). This procedure was modified off of protocols found in literature.253 To an oven dried 2-necked round bottom flask equipped with a condesor and a stir bar was added the sulfonamide (810 mg, 4.33 mmol), acetophenone (1.04g, 8.65 mmol), ZnCl₂ (118 mg, 865 µmol), and Ti(OEt)₄ (4.93 mg, 21.6 mmol). The resulting mixture stirred under vacuum for 15 minutes. Toluene (22.0 mL) was then added and the solution was heated to reflux for 48 h. The solution was then cooled to 0 °C followed by the addition of MeOH (13 mL), DCM (13 mL), and sat aq NaHCO₃ (11 mL). The resulting solid was filtered and washed with dichloromethane. Organic extracts were dried (MgSO₄), filtered, and concentrated. Flash column chromatography of the residue (SiO₂, 5%-40% ethyl acetate in

hexanes) afforded the desired ketimine as a white solid (260 mg, 21%). The characterization data for this compound was found in the literature.\textsuperscript{253}

**General Procedure for (S)-4-Methoxy-N-(1-nitro-2-phenylpropan-2-yl)benzenesulfonamide (63).** To a vial equipped with a stir bar was added the ketimine (15.0 mg, 52.0 µmol), the catalyst (6.80 mg, 10.4 µmol), and dry dichloroethane (416 µL). Nitromethane (6.35 mg, 104 µmol) was then added and the resulting mixture was allowed to stir at rt for 96 h. The reaction mixture was filtered through a silica pad with dichloromethane and ethyl acetate and concentrated in vacuo. Flash column chromatography of the residue (SiO\textsubscript{2}, 25-35% ethyl acetate in hexanes) yielded the desired adduct as a white amorphous solid (4.9 mg, 27%). The major enantiomer was determined to be 11% ee by chiral HPLC analysis. Chiral HPLC analysis (Chiralpak IA, 20% isopropyl alcohol/hexanes, 1.0 mL/min, \(t_r(e_1, \text{major}) = 15.2\) min, \(t_r(e_2, \text{minor}) = 16.2\) min); \(R_f = 0.26\) (33% EtOAc/hexanes); \(^1\)H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta 7.67\) (dd, \(J = 6.6\) Hz, 1.8 Hz, 2 H), 7.29 (m, 5H), 6.89 (dd, \(J = 7.2\) Hz, 1.8 Hz, 2H), 5.88 (br s, 1H), 4.88 (AB system, \(J = 13.2\) Hz, 2H), 3.86 (s, 3H), 1.70 (s, 3H); \(^{13}\)C NMR (150.9 MHz, CDCl\textsubscript{3}) ppm 162.9, 139.7, 133.7, 129.2, 128.9, 128.4, 125.3, 114.1, 82.8, 60.0, 55.6, 24.7; HRMS (ESI): Exact mass calcd for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}NaOS \([M+Na]^+\) 373.0834, found 373.0849.

**General Procedure for (S)-4-Nitro-N-(1-nitro-2-phenylpropan-2-yl)benzenesulfonamide (64).** To a vial equipped with a stir bar was added the ketimine (6.00 mg, 19.7 µmol), the catalyst (1.30 mg, 1.97 µmol), and dry dichloroethane (158 µL). Nitromethane (2.40 mg, 39.4 µmol) was then added and the resulting mixture was allowed to stir at rt for 20 h. The reaction mixture was filtered through a silica pad with dichloromethane and ethyl acetate and concentrated in vacuo. Flash column chromatography of the residue (SiO\textsubscript{2}, 25-50% ethyl acetate in hexanes) yielded the
desired adduct as a white amorphous solid (3.1 mg, 43%). The major enantiomer was determined to be 12% ee by chiral HPLC analysis. Chiral HPLC analysis (Chiralpak IA, 20% isopropyl alcohol/hexanes, 1.0 mL/min, \( t_r(e_1, \text{major}) = 18.7 \text{ min} \), \( t_r(e_2, \text{minor}) = 19.8 \text{ min} \); \( R_f = 0.32 \) (33% EtOAc/hexanes); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta 8.20 \text{ (d, } J = 9.0 \text{ Hz, } 2\text{H}), 7.74 \text{ (d, } J = 9.0 \text{ Hz, } 2\text{H}), 7.27 \text{ (m, } 1\text{H}), 7.22 \text{ (m, } 4\text{H}), 6.12 \text{ (br s, } 1\text{H}), 4.88 \text{ (AB system, } J = 12.6 \text{ Hz, } 2\text{H}), 1.81 \text{ (s, } 3\text{H}); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 147.4, 138.0, 128.9, 128.9, 128.3, 125.8, 124.0, 83.3, 60.1, 24.6.

\[
\begin{align*}
\text{2-}((1R,2R)-2-((4\text{-Chloroquinolin-2-yl)amino)cyclohexyl})isoindoline-1,3-dione (74).} \quad &\text{A flame dried flask equipped with a stir bar was charged with Pd(dba)}_2 \text{ (208 mg, 362 µmol), rac-BINAP (225 mg, µmol), cesium carbonate (8.84 g, 27.1 mmol), the amine (2.21 g, 9.05 mmol), and 2,4-dichloroquinoline (1.79 g, 9.05 mmol). An oven dried condenser was attached and the apparatus was purged twice with argon. Toluene (45 mL) was added and the resulting solution was stirred under reflux for 27 h. The reaction mixture was then cooled to rt, filtered through a Celite pad with CH}_2\text{Cl}_2 \text{ and EtOAc, and concentrated. Flash column chromatography of the residue afforded the desired product as a light yellow foam (1.53 g, 42%).} \quad [\alpha]_{D}^{20} +96 \text{ (c 0.68, CHCl}_3\text{); } R_f = 0.31 \text{ (20% EtOAc/hexanes);} \quad \text{IR (film) 3381, 3060, 2935, 2858, 1767, 1705, 1606, 1567, 1531 cm}^{-1}; \quad \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.65 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H}), 7.49 \text{ (m, } 3\text{H}), 7.38 \text{ (ddd, } J = 8.0, 6.8, 1.2 \text{ Hz, } 1\text{H}), 7.31 \text{ (dd, } J = 5.6, 3.2 \text{ Hz, } 2\text{H}), 7.06 \text{ (ddd, } J = 8.0, 8.0, 1.2 \text{ Hz, } 1\text{H}), 6.59 \text{ (s, } 1\text{H}), 4.84 \text{ (ddddd, } J = 10.8, 10.8, 10.8, 4.0 \text{ Hz, } 1\text{H}), 4.74 \text{ (d, } J = 10.0 \text{ Hz, } 1\text{H}), 4.08 \text{ (ddd, } J = 10.8, 10.8, 4.0 \text{ Hz, } 1\text{H}), 2.66 \text{ (dddd, } J = 12.8, 12.8, 12.8, 3.6 \text{ Hz, } 1\text{H}), 2.23 \text{ (br m, } 1\text{H}), 1.85 \text{ (m, } 3\text{H}), 1.66 \text{ (dddd, } J = 13.2, 13.2, 3.2, 3.2 \text{ Hz, } 1\text{H}), 1.42-1.30 \text{ (m, } 2\text{H)}; \quad \text{C NMR (125.8 MHz, CDCl}_3\text{)} \text{ ppm 168.8, 156.0, 148.1, 142.3, 133.1, 131.3, 129.9, 126.3, 123.3, 122.4, 122.3, 120.9, 111.0, 56.1, 51.3, 33.4, 28.7, 25.5, 24.8; HRMS (ESI) Exact mass calcd for } \text{C}_{23}\text{H}_{21}\text{ClN}_3\text{O}_2 [\text{M+H}]^+ 406.1322, \text{ found 406.1308.}
\end{align*}

(1R,2R)-N1-(4-Chloroquinolin-2-yl)cyclohexane-1,2-diamine (75). To a flask equipped with a stir bar was added the quinoline (596 mg, 1.47 mmol) and ethanol (3 mL), and the resulting solution was allowed to stir at rt for 5 min. Hydrazine monohydrate (264 µL, 5.43 mmol) was added and the reaction mixture was stirred under reflux for 3 h whereupon a white solid precipitated out of solution. After cooling the reaction mixture to rt, the solid was washed with ether and filtered. The remaining solid was triturated with ether, filtered once more and the filtrate was concentrated to an orange foam (401 mg, 99%). \[\alpha\]D20 = -3.3 (c 0.61, CHCl3); Rf = 0.25 (10% MeOH/1%AcOH/CH2Cl2); IR (film) 3268, 2930, 2857, 1609, 1538 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl3) δ 7.91 (d, \(J = 8.0 \) Hz, 1H), 7.61 (d, \(J = 8.4 \) Hz, 1H), 7.49 (ddd, \(J = 8.4, 8.4, 1.2 \) Hz, 1H), 7.20 (ddd, \(J = 8.0, 8.0, 0.8 \) Hz, 1H), 6.75 (s, 1H), 5.19 (d, \(J = 8.4 \) Hz, 1H), 3.64 (m, 1H), 2.44 (ddd \(J = 10.0, 10.0, 4.0 \) Hz, 1H), 2.07 (br m, 1H), 1.90 (br m, 1H), 1.69-1.64 (br m, 4H), 1.39-1.14 (m, 3H), 1.07 (ddd, \(J = 12.8, 12.8, 3.2 \) Hz, 1H); \(^{13}\)C NMR (125.8 MHz, CDCl3) ppm 156.7, 148.5, 142.4, 130.2, 126.1, 123.7, 122.3, 121.3, 111.0, 57.4, 55.8, 35.2, 32.5, 24.9, 24.8; HRMS (ESI) Exact mass calcd for C\(_{15}\)H\(_{19}\)ClN\(_3\) [M+H]+ 276.1268, found 276.1260.

N-((1R,2R)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)-2-(pyrrolidine-1-carbonyl)benzamide (78). A 0.5–2 mL microwave vial was charged with the 4-chloroquinoline (200 mg, 492 µmol), pyrrolidine (162 µL, 1.97 mmol), and trifluorotoluene (2.00 mL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq
NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a yellow foam (201 mg, 80%). $[\alpha]_{D}^{20} +166$ (c 0.90, CHCl₃); Rf = 0.18 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3313, 3054, 2932, 2868, 1621, 1590, 1535 cm⁻¹; $^1$H NMR (600 MHz, CDCl₃) δ 8.47 (br s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.55 (br d, J = 6.6 Hz, 1H), 7.39 (dd, J = 7.2, 7.2 Hz, 1H), 7.23 (dd, J = 7.2, 7.2 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.06 (dd, J = 7.2, 7.2 Hz, 2H), 6.78 (br s, 1H), 5.68 (s, 1H), 4.63 (br s, 1H), 4.16 (m, 1H), 3.75 (br s, 1H), 3.62-3.52 (m, 6H), 3.08 (m, 1H), 3.01 (m, 1H), 1.97 (m, 4H), 1.84-1.74 (m, 5H), 1.65 (m, 1H), 1.40 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl₃) ppm 169.9, 167.4, 157.9, 153.9, 149.4, 137.5, 132.8, 130.2, 128.7, 128.3, 127.6, 126.7, 126.3, 124.8, 119.8, 118.6, 91.8, 57.4, 53.3, 52.0, 48.5, 45.4, 33.1, 32.0, 25.8, 25.6, 25.1, 24.4; HRMS (ESI): Exact mass calcd for C₃₁H₃₈N₅O₂ [M+H]+ 512.3026, found 512.3005.

$N$-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl)benzamide (80a). To a flame dried flask equipped with a stir bar was added the amine (200 mg, 725 µmol), the carboxylic acid (187 mg, 725 µmol), and dichloromethane (4 mL). The resulting solution was chilled to 0 °C and EDC (181 mg, 943 µmol) and DMAP (9.00 mg, 72.5 µmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 20 h, the reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organic layers were washed once with water, dried over MgSO₄, and concentrated. Flash column chromatography of the residue (SiO₂, 5-40% ethyl acetate in hexanes) afforded the desired amide as a white amorphous solid (291 mg, 78%). $[\alpha]_{D}^{20} +291$ (c 1.11, CHCl₃); Rf = 0.43 (30% EtOAc/hexanes); IR (film) 3335, 2937, 2861, 1654, 1608, 1536 cm⁻¹; $^1$H NMR (600 MHz, CDCl₃) δ 8.60 (br d, J = 5.4 Hz, 1H), 7.94 (s, 2H), 7.93 (dd, J = 9.0, 0.6 Hz, 1H), 7.74 (s, 1H), 7.61 (d, 7.8 Hz, 1H), 7.55 (ddd, J = 7.8, 7.8, 0.6 Hz, 1H), 7.29 (ddd, J = 7.8, 7.8, 0.6 Hz, 1H), 6.71 (s, 1H), 4.70 (d, J = 7.2 Hz, 1H), 4.26 (m, 1H), 3.86 (m, 1H), 2.46 (m, 1H), 2.12 (m, 1H), 1.90 (br dd, J = 5.4, 1.8 Hz, 1H), 1.83 (br s, 1H), 1.47 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl₃) ppm 164.9, 156.8, 147.6, 143.3, 137.0, 131.7 (q, $J_{FC} = 34.0$ Hz), 131.2, 127.1, 125.7, 124.5 (q, $J_{FC} = 3.5$ Hz), 124.1, 123.4, 122.7
(q, $J_{FC} = 273.0$ Hz), 121.7, 112.1, 58.9, 53.4, 33.2, 32.1, 25.3, 24.3; HRMS (ESI): Exact mass calcd for $C_{24}H_{21}ClF_6N_3O [M+H]^+$ 516.1278, found 516.1254.

$N$-((1$R$,2$R$)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl)benzamide (78a). A 2-5 mL microwave vial was charged with the 4-chloroquinoline (291 mg, 564 µmol), pyrrolidine (185 µL, 2.26 mmol), and trifluorotoluene (3.52 mL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried over MgSO$_4$ and concentrated to afford a white amorphous solid (215 mg, 69%). $[\alpha]_{D}^{20} +184$ (c 0.93, CHCl$_3$); $R_f = 0.15$ (5% MeOH/1% AcOH/CH$_2$Cl$_2$); IR (film) 3343, 2935, 2861, 1655, 1589, 1531 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 9.52 (d, $J = 4.2$ Hz, 1H), 7.98 (s, 2H), 7.96 (dd, $J = 8.4$, 0.6 Hz, 1H), 7.73 (s, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.39 (ddd, $J = 8.4$, 8.4, 1.2 Hz, 1H), 7.07 (ddd, $J = 8.4$, 7.2, 1.2 Hz, 1H), 5.65 (s, 1H), 4.34 (br s, 1H), 4.21 (m, 1H), 3.73 (m, 1H), 3.55 (m, 4H), 2.51 (d, $J = 12.0$ Hz, 1H), 2.07 (m, 1H), 1.98 (m, 4H), 1.87 (d, $J = 4.8$ Hz, 1H), 1.81 (d, $J = 6.0$ Hz, 1H), 1.44 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 165.2, 158.3, 154.0, 149.0, 137.6, 131.5 (q, $J_{FC} = 33.7$ Hz), 129.3, 127.3, 126.1, 124.9, 124.2, 122.8 (q, $J = 273.1$ Hz), 120.3, 118.6, 91.2, 59.6, 53.1, 51.9, 33.3, 31.9, 25.8, 25.5, 24.4; HRMS (ESI) Exact mass calcd for $C_{28}H_{29}F_6N_4O [M+H]^+$ 551.2246, found 551.2237.

$N$-((1$R$,2$R$)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)benzamide (80b). To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 µmol), benzoic acid (26.6 mg,
218 µmol), and dichloromethane (2 mL). The resulting solution was chilled to 0 °C and EDC (54.3 mg, 283 µmol) and DMAP (2.70 mg, 22.0 µmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 30 h, the reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organic layers were washed once with water, dried over MgSO₄, and concentrated. Flash column chromatography of the residue (SiO₂, 10-50% ethyl acetate in hexanes) afforded the desired amide as a white amorphous solid (65.2 mg, 79%).

\[ \alpha \]₂₀° +433 (c 0.42, CHCl₃); \( R_f = 0.23 \) (30% EtOAc/hexanes); IR (film) 3305, 3061, 2933, 2857, 1643, 1608, 1574, 1537 cm⁻¹; \(^1\)H NMR (600 MHz, CDCl₃) \( \delta 8.18 \) (br d, \( J = 5.4 \) Hz, 1H), 7.94 (dd, \( J = 8.4, 1.2 \) Hz, 1H), 7.74 (d, \( J = 8.4 \) Hz, 1H), 7.62 (ddd, \( J = 8.4, 7.2, 1.8 \) Hz, 1H), 7.52 (dd, \( J = 7.8, 0.6 \) Hz, 2H), 7.30 (ddd, \( J = 8.4, 6.6, 1.2 \) Hz, 1H), 7.25 (dd, \( J = 7.2, 7.2 \) Hz, 1H), 7.04 (d, \( J = 7.8 \) Hz, 2H), 6.68 (s, 1H), 5.04 (br d, \( J = 7.8 \) Hz, 1H), 4.28 (m, 1H), 3.86 (m, 1H), 2.46 (d, \( J = 12.0 \) Hz, 1H), 2.16 (m, 1H), 1.88 (br dd, \( J = 6.0, 1.8 \) Hz, 1H), 1.82 (br dd, \( J = 4.8, 1.8 \) Hz, 1H), 1.48 (m, 4H); \(^{13}\)C NMR (150.9 MHz, CDCl₃) ppm 167.3, 156.9, 148.1, 142.3, 134.2, 130.9, 130.6, 128.1, 126.8, 126.1, 124.2, 122.9, 121.8, 112.5, 58.0, 53.4, 33.1, 32.4, 25.3, 24.5; HRMS (ESI): Exact mass calcd for C₂₂H₂₃ClN₃O \([M+H]^+\) 380.1530, found 380.1543.

\[ \alpha \]₂₀° +225 (c 0.47, CHCl₃); \( R_f = 0.12 \) (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3325, 2930, 2857, 1644, 1588, 1533 cm⁻¹; \(^1\)H NMR (600 MHz, CDCl₃) \( \delta 8.89 \) (br s, 1H), 7.98 (d, \( J = 7.8 \) Hz, 1H), 7.68 (d, \( J = 7.8 \) Hz, 1H), 7.52 (d, \( J = 7.8 \) Hz, 2H), 7.48 (ddd, \( J = 8.4, 7.2, 1.2 \) Hz, 1H), 7.21

\( N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)benzamide \) (78b). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (48.0 mg, 128 µmol), pyrrolidine (42.2 µL, 514 µmol), and trifluorotoluene (1.5 mL). This suspension was heated at 150 °C and stirred in the microwave for 2 h. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried over MgSO₄ and concentrated to afford a light yellow amorphous solid (25.6 mg, 48%).

\[ \alpha \]₂₀° +225 (c 0.47, CHCl₃); \( R_f = 0.12 \) (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3325, 2930, 2857, 1644, 1588, 1533 cm⁻¹; \(^1\)H NMR (600 MHz, CDCl₃) \( \delta 8.89 \) (br s, 1H), 7.98 (d, \( J = 7.8 \) Hz, 1H), 7.68 (d, \( J = 7.8 \) Hz, 1H), 7.52 (d, \( J = 7.8 \) Hz, 2H), 7.48 (ddd, \( J = 8.4, 7.2, 1.2 \) Hz, 1H), 7.21
(dd, \(J = 7.8, 7.8\) Hz, 1H), 7.10 (ddd, \(J = 8.4, 7.2, 1.2\) Hz, 1H), 6.99 (dd, \(J = 7.8, 7.8\) Hz, 2H), 5.61 (s, 1H), 4.52 (br s, 1H), 4.30 (m, 1H), 3.74 (m, 1H), 3.48 (m, 4H), 2.51 (d, \(J = 12.0\) Hz, 1H), 2.09 (d, \(J = 7.2\) Hz, 1H), 1.94 (m, 4H), 1.85 (d, \(J = 3.6\) Hz, 1H), 1.78 (d, \(J = 8.4\) Hz, 1H), 1.41 (m, 4H); \(^{13}\text{C}\) NMR (150.9 MHz, CDCl\(_3\)) ppm 167.2, 158.3, 153.8, 149.4, 134.6, 130.5, 128.8, 127.9, 127.0, 126.5, 125.0, 119.9, 118.8, 91.8, 59.0, 52.5, 33.3, 32.1, 25.8, 25.5, 24.5; HRMS (ESI): Exact mass calcd for C\(_{26}\)H\(_{31}\)N\(_4\)O [M+H]\(^+\) 415.2499, found 415.2480.

**N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-1-naphthamide (80c).** To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 \(\mu\)mol), the carboxylic acid (37.5 mg, 218 \(\mu\)mol), and dichloromethane (2 mL). The resulting suspension was chilled to 0 °C and EDC (54.3 mg, 283 \(\mu\)mol) and DMAP (2.70 mg, 22.0 \(\mu\)mol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 30 h, the reaction mixture was diluted with water and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed once with water, dried over MgSO\(_4\), and concentrated. Flash column chromatography of the residue (SiO\(_2\), 10-40% ethyl acetate in hexanes) afforded the desired amide as a white solid (48.4 mg, 52%). Mp 208.0-210.0 °C; \([\alpha]_{D}^{20} +292\) (c 0.49, CHCl\(_3\)); \(R_f = 0.40\) (40% EtOAc/hexanes); IR (film) 3296, 3058, 2952, 2862, 1642, 1607, 1575, 1536 cm\(^{-1}\); \(^1\text{H}\) NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.17 (d, \(J = 8.4\) Hz, 1H), 7.89 (dd, \(J = 8.4, 0.6\) Hz, 1H), 7.80 (br d, \(J = 6.6\) Hz, 1H), 7.68 (d, \(J = 7.8\) Hz, 1H), 7.64 (d, \(J = 8.4\) Hz, 1H), 7.36 (dddd, \(J = 9.0, 6.6, 4.8, 1.2\) Hz, 2H), 7.32 (ddd, \(J = 8.4, 6.6, 1.2, 1\)H), 7.21 (m, 2H), 6.97 (dd, \(J = 6.6, 0.6\) Hz, 1H), 6.89 (dd, \(J = 8.4, 8.4\) Hz, 1H), 6.72 (s, 1H), 5.07 (d, \(J = 7.2\) Hz, 1H), 4.22 (m, 1H), 4.02 (m, 1H), 2.50 (br d, \(J = 11.4\) Hz, 1H), 2.20 (br m, 1H), 1.87 (m, 2H), 1.48 (m, 4H); \(^{13}\text{C}\) NMR (150.9 MHz, CDCl\(_3\)) ppm 169.9, 156.5, 147.9, 142.9, 134.4, 133.4, 130.4, 130.0, 129.9, 128.0, 126.6, 125.98, 125.97, 125.2, 124.5, 124.4, 123.8, 122.7, 121.5, 112.2, 57.1, 54.0, 33.0, 32.6, 25.2, 24.6; HRMS (ESI): Exact mass calcd for C\(_{26}\)H\(_{25}\)ClN\(_3\)O [M+H]\(^+\) 430.1686, found 430.1673.
N-((1R,2R)-2-((4-(Pyrrlolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)-1-naphthamide (78c). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (30.0 mg, 69.8 µmol), pyrrolidine (23.0 µL, 279 µmol), and trifluorotoluene (446 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a light yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a tan amorphous solid (17.6 mg, 54%). \([\alpha]_D^{20} +172 (c 0.79, \text{CHCl}_3); R_f = 0.39 (5\% \text{ MeOH}/1\% \text{ AcOH}/\text{CH}_2\text{Cl}_2); \text{IR} \ (\text{film}) 3329, 3047, 2930, 2857, 1643, 1588, 1532 \text{ cm}^{-1};^1\text{H NMR} (600 \text{ MHz, CDCl}_3) \delta 8.65 \text{ (br s, 1H)}, 8.33 \text{ (dd, } J = 9.0, 1.8 \text{ Hz, 1H)}, 7.94 \text{ (d, } J = 8.4 \text{ Hz, 1H)}, 7.69 \text{ (dd, } J = 9.0, 1.8 \text{ Hz, 1H)}, 7.60 \text{ (d, } J = 8.4 \text{ Hz, 1H)}, 7.36 \text{ (m, 2H)}, 7.20 \text{ (br dd, } J = 7.2, 7.2 \text{ Hz, 1H)}, 7.14 \text{ (br s, 1H)}, 7.02 \text{ (dd, } J = 7.2, 7.2 \text{ Hz, 1H)}, 6.81 \text{ (br s, 1H)}, 6.70 \text{ (br s, 1H)}, 5.70 \text{ (s, 1H)}, 4.60 \text{ (br s, 1H)}, 4.26 \text{ (br s, 1H)}, 3.89 \text{ (br d, } J = 5.4 \text{ Hz, 1H)}, 3.51 \text{ (br m, 4H)}, 2.56 \text{ (br d, } J = 7.8 \text{ Hz, 1H)}, 2.14 \text{ (br d, } J = 5.4 \text{ Hz, 1H)}, 1.96 \text{ (m, 4H)}, 1.88 \text{ (br s, 1H)}, 1.82 \text{ (br s, 1H)}, 1.49 \text{ (m, 4H)};^1\text{C NMR} (150.9 \text{ MHz, CDCl}_3) \text{ ppm } 169.7, 157.9, 154.0, 149.1, 134.4, 133.5, 130.2, 129.6, 128.6, 127.9, 126.4, 125.8, 125.7, 124.9, 124.7, 124.4, 119.8, 118.5, 91.7, 58.5, 52.7, 51.9, 33.3, 32.4, 25.8, 25.4, 24.6; \text{HRMS (ESI)}: \text{Exact mass calcd for C}_{30}\text{H}_{33}\text{N}_{4}\text{O} [\text{M+H}]^+ 465.2654, \text{found 465.2672.}

N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-3,5-dimethylbenzamide (80d). To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 µmol), the carboxylic acid (32.7 mg, 218 µmol), and dichloromethane (2 mL). The resulting solution was chilled to 0 °C
and EDC (54.3 mg, 283 µmol) and DMAP (2.70 mg, 22.0 µmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 30 h, the reaction mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were washed once with water, dried over MgSO$_4$, and concentrated. Flash column chromatography of the residue (SiO$_2$, 10-40% ethyl acetate in hexanes) afforded the desired amide as a white amorphous solid (66.9 mg, 75%). $[\alpha]_D^{20} +387$ (c 0.45, CHCl$_3$); $R_f = 0.34$ (40% EtOAc/hexanes); IR (film) 3303, 3060, 2929, 2857, 2361, 1643, 1605, 1574, 1536 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.00 (br d, $J = 6.6$ Hz, 1H), 7.93 (dd, $J = 7.8$, 0.6 Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.57 (ddd, $J = 8.4$, 7.2, 1.2 Hz, 1H), 7.27 (ddd, $J = 7.8$, 7.8, 0.6 Hz, 1H), 7.02 (s, 2H), 6.87 (s, 1H), 6.69 (s, 1H), 5.22 (d, $J = 7.8$ Hz, 1H), 4.33 (m, 1H), 3.87 (m, 1H), 2.44 (d, $J = 13.2$ Hz, 1H), 2.15 (m, 1H), 1.94 (s, 6H), 1.83 (m, 1H), 1.57-1.36 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 167.9, 157.0, 148.2, 142.7, 137.9, 134.3, 132.6, 130.7, 126.2, 124.5, 124.1, 122.8, 121.7, 112.6, 58.0, 53.0, 33.0, 32.4, 25.4, 24.6, 20.8; HRMS (ESI) Exact mass calcd for C$_{24}$H$_{27}$N$_3$O[M+H]$^+$ 408.1843, found 408.1847.

3,5-Dimethyl-N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)benzamide (78d). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (40.0 mg, 98.1 µmol), pyrrolidine (32.0 µL, 392 µmol), and trifluorotoluene (620 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried over MgSO$_4$ and concentrated to afford a yellow amorphous solid (23.7 mg, 55%). $[\alpha]_D^{20} +238$ (c 0.75, CHCl$_3$); $R_f = 0.51$ (10% MeOH/1% AcOH/CH$_2$Cl$_2$); IR (film) 3320, 2929, 2858, 2361, 1643, 1590, 1533 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.68 (br s, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.43 (ddd, $J = 7.8$, 7.8, 0.6 Hz, 1H), 7.08 (ddd, $J = 8.4$, 8.4, 1.2 Hz, 1H), 7.05 (s, 2H), 6.85 (s, 1H), 5.64 (s, 1H), 4.49 (br s, 1H), 4.33 (br m, 1H), 3.74 (m, 1H), 1.94 (s, 6H), 1.83 (m, 1H), 1.57-1.36 (m, 4H).
3.50 (br m, 4H), 2.49 (d, \( J = 11.4 \) Hz, 1H), 2.07 (br d, \( J = 2.4 \) Hz, 1H), 1.95 (br m, 4H), 1.91 (s, 6H), 1.84 (br d, \( J = 3.0 \) Hz, 1H), 1.78 (br d, \( J = 6.0 \) Hz, 1H), 1.46-1.35 (m, 4H); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 167.8, 158.3, 153.9, 149.5, 137.7, 134.8, 132.2, 129.0, 126.7, 125.0, 124.7, 120.0, 118.9, 91.9, 58.9, 52.3, 51.9, 33.4, 32.2, 25.8, 25.6, 24.5, 20.7; HRMS (ESI) Exact mass calcd for C\(_{28}\)H\(_{35}\)N\(_4\)O [M+H]\(^+\) 443.2811, found 443.2813.

\(N\)-((1\(R\),2\(R\))-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-2-naphthamide (80e). To a flame dried flask equipped with a stir bar was added the amine (61.0 mg, 221 \( \mu \)mol), the carboxylic acid (38.1 mg, 221 \( \mu \)mol), and dichloromethane (2 mL). The resulting suspension was chilled to 0 °C and EDC (55.2 mg, 288 \( \mu \)mol) and DMAP (2.70 mg, 22.0 \( \mu \)mol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 30 h, the reaction mixture was diluted with water and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed once with water, dried (MgSO\(_4\)), and concentrated. Flash column chromatography of the residue (SiO\(_2\), 10-40% ethyl acetate in hexanes) afforded the desired amide as a white solid (68.8 mg, 72%). 

\([\alpha]_D^{20} + 318 \) (c 0.42, CHCl\(_3\)); \( R_f = 0.40 \) (40% EtOAc/hexanes); IR (film) 3305, 3058, 2932, 2857, 2361, 1643, 1607, 1572, 1537 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta 8.36 \) (br d, \( J = 6.6 \) Hz, 1H), 7.96 (dd, \( J = 8.4, 1.2 \) Hz, 1H), 7.79 (d, \( J = 8.4 \) Hz, 1H), 7.76 (s, 1H), 7.69 (dd, \( J = 9.0, 2.4 \) Hz, 2H), 7.62 (ddd, \( J = 8.4, 7.2, 1.8 \) Hz, 1H), 7.57 (d, \( J = 8.4 \) Hz, 1H), 7.41 (ddd, \( J = 7.8, 7.2, 1.2 \) Hz, 1H), 7.33 (ddd, \( J = 8.4, 8.4, 1.2 \) Hz, 1H), 7.29 (ddd, \( J = 7.8, 7.8, 0.6 \) Hz, 1H), 7.05 (d, \( J = 8.4 \) Hz, 1H), 6.71 (s, 1H), 5.15 (d, \( J = 7.8 \) Hz, 1H), 4.37 (m, 1H), 3.93 (m, 1H), 2.53 (d, \( J = 12.0 \) Hz, 1H), 2.17 (br m, 1H), 1.90 (dd, \( J = 6.0, 1.8 \) Hz, 1H), 1.84 (dd, \( J = 5.4, 1.2 \) Hz, 1H), 1.58-1.42 (m, 4H); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 167.5, 157.0, 148.1, 142.9, 134.4, 132.2, 131.6, 130.8, 128.8, 128.0, 127.4, 127.2, 126.8, 126.2, 126.1, 124.3, 123.9, 122.9, 121.8, 112.6, 58.4, 53.2, 33.1, 32.5, 25.4, 24.5; HRMS (ESI): Exact mass calcd for C\(_{28}\)H\(_{25}\)ClN\(_3\)O [M+H]\(^+\) 430.1686, found 430.1668.
**N-((1R,2R)-2-((4-(Pyrroldin-1-yl)quinolin-2-yl)amino)cyclohexyl)-2-naphthamide (78e).** A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (35.0 mg, 81.4 µmol), pyrrolidine (27.0 µL, 326 µmol), and trifluorotoluene (520 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a light yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a light yellow amorphous solid (21.2 mg, 56%). \([\alpha]_{D}^{20} +150 (c 0.91, \text{CHCl}_3)\); \(R_f=0.39 (5\% \text{ MeOH}/1\% \text{ AcOH}/\text{CH}_2\text{Cl}_2)\); IR (film) 3324, 3054, 2937, 2361, 1644, 1588, 1533, 1502 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 9.00 (\text{br s, 1H}), 8.02 (\text{d, } J = 8.4 \text{ Hz, 1H}), 7.76 (\text{s, 1H}), 7.73 (\text{m, 2H}), 7.68 (\text{d, } J = 8.4 \text{ Hz, 1H}), 7.53 (\text{d, } J = 8.4 \text{ Hz, 1H}), 7.48 (\text{ddd, } J = 8.4, 7.2, 1.2 \text{ Hz, 1H}), 7.39 (\text{ddd, } J = 7.8, 7.8, 1.2 \text{ Hz, 1H}), 7.26 (\text{ddd, } J = 7.2, 7.2 \text{ Hz, 1H}), 7.15 (\text{dd, } J = 7.2, 7.2 \text{ Hz, 1H}), 6.95 (\text{d, } J = 7.8 \text{ Hz, 1H}), 5.61 (\text{s, 1H}), 4.62 (\text{br s, 1H}), 4.39 (\text{m, 1H}), 3.82 (\text{m, 1H}), 3.42 (\text{m, 4H}), 2.55 (\text{br d, } J = 12.0 \text{ Hz, 1H}), 2.12 (\text{d, } J = 10.2 \text{ Hz, 1H}), 1.86 (\text{m, 5H}), 1.82 (\text{br m, 1H}), 1.56-1.41 (\text{m, 4H}); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 167.4, 158.5, 153.8, 149.5, 134.3, 132.4, 132.0, 129.1, 129.0, 127.7, 127.2, 126.9, 126.7, 125.8, 125.2, 124.3, 120.0, 118.9, 91.8, 59.3, 52.4, 51.9, 33.3, 32.7, 25.7, 25.6, 24.6; HRMS (ESI): Exact mass calcd for C\(_{30}\)H\(_{33}\)N\(_4\)O [M+H]\(^+\) 465.2654, found 465.2646.

**N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)picolinamide (80f).** To a flame dried flask equipped with a stir bar was added the amine (40.0 mg, 145 µmol), picolinic acid (17.9 mg, 145 µmol), and dichloromethane (1 mL). The resulting solution was chilled to 0 °C and EDC (36.2
mg, 189 µmol) and DMAP (1.80 mg, 15.0 µmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 14 h, the reaction mixture was diluted with water and extracted with CH₂Cl₂. The combined organic layers were washed once with water, dried (MgSO₄), and concentrated. Flash column chromatography of the residue (SiO₂, 40-80% ethyl acetate in hexanes) afforded the desired amide as a viscous yellow oil (29.7 mg, 54%). 

\[ [\alpha]_{D}^{20} +158 \ (c \ 0.59, \text{CHCl}_3); \ R_f = 0.14 \ (20\% \text{EtOAc/hexanes}); \ IR \ (\text{film}) \ 3319, 2932, 2857, 1658, 1609, 1570, 1534 \text{ cm}^{-1}; \ ^1H \text{ NMR} \ (600 \text{MHz, CDCl}_3) \ \delta \ 8.87 \text{ (br d, J = 7.2 Hz, 1H), 8.04 \text{ (dd, J = 6.6, 0.6 Hz, 1H), 7.86 \text{ (dd, J = 8.4, 1.2 Hz, 1H), 7.79 \text{ (d, J = 7.8 Hz, 1H), 7.68 \text{ (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.57 \text{ (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.23 \text{ (ddd, J = 8.4, 7.2, 1.2 Hz, 1H}, 7.17 \text{ (m, 1H), 6.64 \text{ (s, 1H), 5.17 \text{ (d, J = 7.2 Hz, 1H), 4.26 \text{ (ddd, J = 11.4, 11.4, 7.8, 4.2 Hz, 1H), 3.94 \text{ (ddd, J = 10.8, 10.8, 7.8, 3.6 Hz, 1H), 2.28 \text{ (m, 2H), 1.85 \text{ (dd, J = 12.0, 1.8 Hz, 2H), 1.57-1.44 \text{ (m, 3H), 1.43-1.34 \text{ (m, 1H); \ ^13C \text{ NMR} \ (100.6 \text{MHz, CDCl}_3) \ ppm \ 165.0, 156.3, 149.7, 148.6, 147.7, 142.2, 136.8, 130.0, 126.8, 125.7, 123.7, 122.4, 121.8, 121.4, 112.1, 55.5, 54.6, 32.7, 32.4, 24.9, 24.8; \ HRMS \ (ESI) \ Exact \ mass \ calcld \ for \ C_{21}H_{22}ClN_4O \ [M+H]^+ \ 381.1482, \ found \ 381.1495.} \]

A 2-5 mL microwave vial was charged with the 4-chloroquinoline (50.0 mg, 131 µmol), pyrrolidine (130 µL, 1.58 mmol), and trifluorotoluene (800 µL). This suspension was heated at 150 °C and stirred in the microwave for 3 h. More pyrrolidine (65.0 µL, 788 µmol) was added and the reaction mixture was heated to 180 °C and stirred in the microwave for an additional 1.5 h. The reaction was concentrated and purified by flash column chromatography (1-10% methanol w/ 1% AcOH) to provide a dark-yellow oil. This material was diluted with dichloromethane and washed twice with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried over MgSO₄ and concentrated to afford an off-white amorphous solid (24.7 mg, 45%). 

\[ [\alpha]_{D}^{20} +144 \ (c \ 0.49, \text{CHCl}_3); \ R_f = 0.49 \ (10\% \text{MeOH/1% AcOH/CH}_2\text{Cl}_2); \ IR \ (\text{film}) \ 3337, 2930, 2857, 1657, 1588, 1531 \text{ cm}^{-1}; \ ^1H \text{ NMR} \ (400 \text{MHz, CDCl}_3) \ \delta \ 9.36 \text{ (br d, J = 6.8 Hz, 1H), 8.00 \text{ (d, J = 8.0 Hz, 1H), 7.97 \text{ (br d, J} \]
$= 4.4$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.63 (ddd, $J = 8.0, 8.0, 1.6$ Hz, 1H), 7.46 (ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 7.13 (dd, $J = 6.4, 4.8$ Hz, 1H), 7.04 (br ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 5.61 (s, 1H), 4.52 (br d, $J = 6.8$ Hz, 1H), 4.32 (ddddd, $J = 11.2, 11.2, 8.0, 4.0$ Hz, 1H), 3.84 (br dddd, $J = 10.8, 10.8, 7.6, 4.4$ Hz, 1H), 3.45 (br m, 4H), 2.22 (d, $J = 12.4$ Hz, 1H), 1.92 (m, 4H), 1.81 (br s, 2H), 1.54–1.33 (m, 4H); $^{13}$C NMR ($125.8$ MHz, CDCl$_3$) ppm 164.9, 157.8, 153.7, 150.2, 150.0, 147.8, 136.5, 128.2, 127.4, 125.3, 124.6, 121.6, 119.4, 118.6, 92.0, 56.7, 53.3, 51.8, 33.2, 32.2, 25.7, 25.2, 24.7; HRMS (ESI) Exact mass calcd for C$_{25}$H$_{30}$N$_5$O [M+H]$^+$ 416.2450, found 416.2432.

$N$-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-2,4,6-trimethylbenzamide (80g).

To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 µmol) and dichloromethane (3 mL), immediately followed by the addition of $N,N$-diisopropyl ethylamine (45.0 µL, 261 µmol), the acid chloride (43.0 µL, 261 µmol), and DMAP (2.70 mg, 22.0 µmol). The reaction mixture was stirred at rt for 30 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO$_3$, extracted with dichloromethane, dried (MgSO$_4$), filtered and concentrated. Flash column chromatography of the residue (SiO$_2$, 10-80% ethyl acetate in hexanes) afforded the desired amide as an off white solid (74.1 mg, 81%). Mp 261.0–264.0 °C; $[\alpha]_D^{20}$ +193 ($c$ 0.58, CHCl$_3$); $R_f = 0.46$ (40% EtOAc/hexanes); IR (film) 3250, 3101, 3059, 2930, 2856, 2363, 1642, 1608, 1540 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.93 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.38 (ddd, $J = 7.2, 7.2, 1.2$ Hz, 1H), 7.26 (br s, 1H), 7.22 (m, 2H), 6.71 (s, 1H), 6.56 (s, 2H), 5.25 (br d, $J = 6.0$ Hz, 1H), 4.05 (m, 1H), 3.94 (m, 1H), 2.36 (m, 1H), 2.26 (m, 1H), 2.14 (s, 3H), 1.98 (s, 6H), 1.83 (br m, 2H), 1.48–1.34 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 171.1, 156.1, 148.0, 142.6, 137.9, 134.9, 133.6, 130.2, 127.8, 126.0, 123.8, 122.6, 121.3, 112.1, 55.5, 54.6, 32.8, 32.5, 24.9, 24.6, 21.0, 18.6; HRMS (ESI) Exact mass calcd for C$_{25}$H$_{30}$ClN$_5$O [M+H]$^+$ 422.1999, found 422.1983.
2,4,6-Trimethyl-N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl) benzamide (78g). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (40.0 mg, 94.8 µmol), pyrrolidine (31.0 µL, 379 µmol), and trifluorotoluene (680 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed four times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a tan foam (20.9 mg, 48%). [α]²⁰_D +120 (c 0.43, CHCl₃); Rf = 0.32 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3317, 2926, 2856, 2362, 1644, 1590, 1533 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.55 (br s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.12 (dd, J = 6.6, 6.6 Hz, 1H), 6.99 (dd, J = 7.2, 7.2 Hz, 1H), 6.90 (br d, J = 7.2 Hz, 1H), 6.47 (s, 2H), 5.68 (s, 1H), 4.57 (br s, 1H), 4.03 (br m, 1H), 3.78 (br m, 1H), 3.50 (br m, 2H), 3.50 (br m, 2H), 2.50 (br d, J = 10.8 Hz, 1H), 2.14 (br d, J = 11.4 Hz, 1H), 2.12 (s, 3H), 2.05-1.96 (m, 4H), 1.94 (s, 6H), 1.82 (br s, 1H), 1.78 (br s, 1H), 1.48-1.35 (m, 4H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 170.8, 157.7, 153.9, 149.0, 137.2, 135.4, 133.5, 128.4, 126.1, 124.5, 119.6, 118.3, 91.8, 57.2, 53.4, 51.9, 33.2, 32.3, 25.8, 25.2, 24.4, 21.0, 18.6; HRMS (ESI): Exact mass calcd for C₂₉H₃₆NaNO [M+Na]⁺ 479.2787, found 479.2774.

N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-2,6-dimethoxybenzamide (80h). To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 µmol) and dichloromethane (3 mL), immediately followed by the addition of N,N-diisopropyl ethylamine (45.0 µL, 261 µmol), the acid chloride (52.4 mg, 261 µmol), and DMAP (2.70 mg, 22.0 µmol).
The reaction mixture was stirred at rt for 48 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO₃, extracted with dichloromethane, dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 10-60% ethyl acetate in hexanes) afforded the desired amide as a white solid (68.3 mg, 71%). Mp 256.0-258.0 °C; [α]₂⁰_D +166 (c 0.56, CHCl₃); Rf = 0.16 (40% EtOAc/hexanes); IR (film) 3284, 3060, 2933, 2857, 2361, 1646, 1607, 1538 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.92 (d, J = 8.4 Hz, 1H), 7.42 (m, 2H), 7.21 (ddd, J = 8.4, 6.0, 2.4 Hz, 1H), 7.10 (dd, J = 8.4, 8.4 Hz, 1H), 6.78 (br d, J = 6.6 Hz, 1H), 6.75 (s, 1H), 6.32 (d, J = 8.4 Hz, 2H), 5.50 (d, J = 5.4 Hz, 1H), 4.02 (m, 2H), 3.47 (s, 6H), 2.34 (d, J = 13.2 Hz, 1H), 2.27 (d, J = 10.8 Hz, 1H), 1.82 (dd, J = 6.6, 2.4 Hz, 2H), 1.48-1.32 (m, 4H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 166.7, 157.0, 156.5, 148.5, 141.9, 130.3, 130.2, 126.1, 123.7, 122.3, 121.3, 115.7, 112.7, 103.6, 55.6, 55.5, 54.6, 32.7, 32.4, 24.80, 24.75; HRMS (ESI): Exact mass calcd for C₂₄H₂₇ClN₃O₃ [M+H]⁺ 440.1741, found 440.1746.

2,6-Dimethoxy-N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl) benzamide (78h). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (40.0 mg, 90.9 µmol), pyrrolidine (30.0 µL, 364 µmol), and trifluorotoluene (650 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a tan amorphous solid (18.4 mg, 43%). Mp 238.0-242.0 °C; [α]₂⁰_D +98.6 (c 0.76, CHCl₃); Rf = 0.30 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3287, 2931, 2857, 2361, 1645, 1593, 1533 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.01 (br s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.20 (br dd, J = 7.2, 7.2 Hz, 1H), 7.14 (br d, J = 7.2 Hz, 1H), 7.04 (dd, J = 8.4, 8.4 Hz, 1H), 7.00 (dd, J = 6.6 Hz, 1H), 6.23 (d, J = 7.8 Hz, 2H),
5.75 (s, 1H), 4.70 (br s, 1H), 4.03 (br m, 1H), 3.87 (br m, 1H), 3.57 (br s, 2H), 3.49 (br s, 2H), 3.39 (s, 6H), 2.44 (br d, J = 7.2 Hz, 1H), 2.20 (br d, J = 11.4 Hz, 1H), 2.04-1.95 (m, 4H), 1.80 (br s, 1H), 1.76 (br s, 1H), 1.43-1.36 (br m, 4H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 166.1, 157.8, 157.0, 153.8, 149.4, 129.7, 128.5, 126.2, 124.4, 119.5, 118.5, 116.5, 103.6, 92.4, 56.4, 55.5, 53.7, 52.0, 33.2, 32.2, 25.7, 25.1, 24.5; HRMS (ESI): Exact mass calcd for C$_{28}$H$_{35}$N$_4$O$_3$ [M+H]$^+$ 475.2709, found 475.2726.

$N$-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-2-methyl-6-nitrobenzamide (80i).

To a flame dried flask equipped with a stir bar was added the amine (70.0 mg, 254 µmol) and dichloromethane (3 mL), immediately followed by the addition of $N,N$-diisopropyl ethylamine (53.0 µL, 305 µmol), the acid chloride (66.0 mg, 330 µmol), and DMAP (3.10 mg, 25.4 µmol). The reaction mixture was stirred at rt for 30 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO$_3$, extracted with dichloromethane, dried (MgSO$_4$), filtered and concentrated. Flash column chromatography of the residue (SiO$_2$, 10-40% ethyl acetate in hexanes) afforded the desired amide as a light yellow amorphous solid (98.7 mg, 89%). Mp 200.0-202.0 °C; $[\alpha]_D^{20}$ +302 (c 0.62, CHCl$_3$); $R_f = 0.23$ (40% EtOAc/hexanes); IR (film) 3299, 3059, 2933, 2858, 2361, 1653, 1608, 1533 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.75 (br d, J = 3.0 Hz, 1H), 7.89 (dd, J = 7.8, 1.2 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.23 (ddd, 8.4, 7.2, 1.2 Hz, 1H), 7.17 (dddd, $J = 8.4, 7.2, 1.2$ Hz, 1H), 7.14 (m, 2H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.71 (s, 1H), 5.21 (br d, $J = 6.6$ Hz, 1H), 4.03 (dddd, $J = 10.2, 10.2, 6.6, 3.6$ Hz, 1H), 3.85 (m, 1H), 2.56 (br m, 1H), 2.13 (br dd, $J = 12.0, 2.4$ Hz, 1H), 2.08 (s, 3H), 1.84 (m, 2H), 1.45 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 166.3, 156.7, 147.2, 145.2, 142.7, 137.3, 135.5, 132.7, 130.3, 128.6, 124.9, 123.8, 122.6, 121.5, 121.3, 112.4, 58.1, 53.6, 32.7, 32.0, 25.1, 24.2, 18.4; HRMS (ESI) Exact mass calcd for C$_{23}$H$_{23}$ClN$_4$NaO$_3$ [M+Na]$^+$ 461.1356, found 461.1357.
2-Methyl-6-nitro-N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)benzamide (78i). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (50.0 mg, 114 µmol), pyrrolidine (38.0 µL, 456 µmol), and trifluorotoluene (820 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a dark yellow amorphous solid (38.3 mg, 71%). Mp 217.0-223.0 °C; [α]D²⁰ +193 (c 0.63, CHCl₃); Rf = 0.37 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3329, 2929, 2858, 1653, 1588, 1532 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.82 (br s, 1H), 7.88 (dd, J = 8.4, 0.6 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.09 (m, 2H), 7.00 (br ddd, J = 7.8, 7.8 Hz, 1H), 6.93 (br ddd, J = 7.2, 7.2 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.66 (s, 1H), 4.48 (br s, 1H), 4.00 (m, 1H), 3.72 (m, 1H), 3.54 (m, 4H), 2.63 (br dd, J = 8.4, 1.8 Hz, 1H), 2.10 (s, 3H), 2.08-1.94 (m, 5H), 1.84 (br m, 1H), 1.78 (br m, 1H), 1.42 (m, 4H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 166.2, 158.0, 154.0, 148.3, 145.2, 137.3, 135.3, 133.2, 128.5, 128.2, 125.0, 124.7, 121.4, 119.6, 118.3, 91.6, 59.2, 53.1, 51.9, 33.0, 31.7, 25.8, 25.3, 24.1, 18.4; HRMS (ESI): Exact mass calcd for C₂₇H₃₁N₅O₃ [M+Na]⁺ 496.2325, found 496.2315.

N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)anthracene-9-carboxamide (80j). To a flame dried flask equipped with a stir bar was added the amine (70.0 mg, 254 µmol) and dichloromethane (3 mL), immediately followed by the addition of N,N-diisopropyl ethylamine (53.0 µL, 305 µmol), the acid chloride (79.4 mg, 330 µmol), and DMAP (3.10 mg, 25.4 µmol).
The reaction mixture was stirred at rt for 48 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO₃, extracted with dichloromethane, dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 10-40% ethyl acetate in hexanes) afforded the desired amide as a light yellow foam (87.5 mg, 72%). $[\alpha]_{D}^{20} +169$ (c 0.66, CHCl₃); $R_f = 0.38$ (40% EtOAc/hexanes); IR (film) 3288, 3055, 2932, 2857, 1642, 1607, 1535 cm⁻¹; $^1$H NMR (600 MHz, CDCl₃) δ 8.44 (br s, 1H), 8.20 (s, 1H), 8.13 (br d, $J = 6.0$ Hz, 1H), 7.95 (br d, $J = 7.2$ Hz, 1H), 7.71 (dd, $J = 8.4, 0.6$ Hz, 1H), 7.53 (br s, 2H), 7.45 (br m, 2H), 7.03 (dd, $J = 6.6, 6.6$ Hz, 1H), 6.98 (dd, $J = 6.6, 6.6$ Hz, 1H), 6.95 (br m, 1H), 6.72 (s, 1H), 6.68 (br m, 1H), 6.45 (d, $J = 7.8$ Hz, 1H), 5.23 (d, $J = 5.4$ Hz, 1H), 4.1 (m, 2H), 2.65 (br m, 1H), 2.15 (br m, 1H), 1.86 (br m, 2H), 1.54-1.39 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl₃) ppm 169.7, 156.2, 147.3, 142.8, 132.1, 130.8, 129.9, 128.4, 127.8, 127.6, 127.2, 126.3, 125.6, 125.5, 125.1, 125.0, 124.7, 124.0, 123.5, 122.4, 121.2, 111.9, 57.6, 53.8, 32.8, 32.7, 25.1, 24.4; HRMS (ESI) Exact mass calcd for C₃₀H₂₆ClN₃NaO [M+Na]⁺ 502.1662, found 502.1653.

$N$-((1R,2R)-2-((4-(Pyrrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)anthracene-9-carboxamide (78j). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (50.0 mg, 104 µmol), pyrrolidine (34.0 µL, 417 µmol), and trifluorotoluene (750 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a tan amorphous solid (26.3 mg, 49%). Mp 273.0-278.0 °C; $[\alpha]_{D}^{20} +145$ (c 0.43, CHCl₃); $R_f = 0.35$ (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3331, 3052, 2929, 2856, 1640, 1588, 1531 cm⁻¹; $^1$H NMR (600 MHz, CDCl₃) δ 9.35 (br s, 1H), 8.19 (s, 1H), 8.19 (br s, 1H), 7.95 (br d, $J = 6.0$ Hz, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.52 (br m, 4H), 6.89 (br s, 1H), 6.76 (m, 2H), 6.62 (br s, 1H), 6.21 (br d, $J = 7.8$ Hz,
1H), 5.69 (s, 1H), 4.68 (br s, 1H), 4.09 (br s, 2H), 3.48 (m, 4H), 2.76 (br d, \(J = 6.0 \text{ Hz}, 1\text{H})

To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 \(\mu\text{mol}\)) and dichloromethane (3 mL), immediately followed by the addition of \(N,N-\text{diisopropyl ethylamine (46.0 } \mu\text{L, 261 } \mu\text{mol})\), the acid chloride (86.8 mg, 283 \(\mu\text{mol}\)) and DMAP (2.70 mg, 21.8 \(\mu\text{mol}\)). The reaction mixture was stirred at rt for 18 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO\(_3\), extracted with dichloromethane, dried (MgSO\(_4\)), filtered and concentrated. Flash column chromatography of the residue (SiO\(_2\), 5-40\% ethyl acetate in hexanes) afforded the desired amide an off white solid (105 mg, 88\%). Mp 185.0-188.0 °C; \([\alpha]_{D}^{20} +72.8 (c 0.43, \text{ CHCl}_3)\); \(R_f = 0.47 (40\% \text{ EtOAc/hexanes})\); IR (film) 3334, 3059, 2931, 2361, 1652, 1607, 1533 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta \) 7.95 (dd, \(J = 7.8, 0.6 \text{ Hz}, 1\text{H})\), 7.48 (ddd, \(J = 7.8, 7.8, 0.6 \text{ Hz}, 1\text{H})\), 7.34 (d, \(J = 8.4 \text{ Hz}, 1\text{H})\), 7.25 (ddd, \(J = 7.8, 7.8, 0.6 \text{ Hz}, 1\text{H})\), 7.14-7.07 (m, 15H), 6.55 (s, 1H), 6.46 (d, \(J = 7.2 \text{ Hz}, 1\text{H})\), 5.21 (br d, \(J = 6.6 \text{ Hz}, 1\text{H})\), 4.00 (dddd, \(J = 10.8, 10.8, 7.2, 3.6 \text{ Hz}, 1\text{H})\), 3.93 (dddd, \(J = 11.4, 11.4, 7.8, 4.2, 1\text{H})\), 2.23 (br d, \(J = 13.2 \text{ Hz}, 1\text{H})\), 2.15 (br d, \(J = 13.2 \text{ Hz}, 1\text{H})\), 1.77 (br m, 2H), 1.39 (m, 2H), 1.30-1.22 (m, 2H); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 174.1, 155.9, 148.4, 143.2, 142.3, 130.2, 130.1, 127.7, 126.7, 126.5, 123.8, 122.4, 121.5, 112.3, 67.8, 55.1, 54.5, 32.9, 32.1, 24.7 (2C); HRMS (ESI): Exact mass calcd for C\(_{35}\)H\(_{33}\)ClN\(_3\)O [M+H]\(^{+}\) 546.2312, found 546.2285.
2,2,2-Triphenyl-N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)acetamide (78k). A 0.2-0.5 mL microwave vial was charged with the 4-chloroquinoline (20.0 mg, 36.6 µmol), pyrrolidine (12.0 µL, 146 µmol), and trifluorotoluene (270 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a light yellow amorphous solid (18.1 mg, 85%). Mp 168.0-173.0 °C; [α]D 20 +10.2 (c 0.55, CHCl₃); Rf = 0.44 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3353, 3057, 2927, 2856, 1653, 1589, 1528, 1518, 1496 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 8.4, 0.8 Hz, 1H), 7.32 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.17 (br d, J = 8.0 Hz, 1H), 7.18-7.01 (m, 15H), 6.73 (br d, J = 6.8 Hz, 1H), 5.61 (s, 1H), 4.65 (br s, 1H), 4.02 (ddd, J = 11.2, 11.2, 7.6, 4.0 Hz, 1H), 3.84 (ddd, J = 11.2, 11.2, 7.6, 3.6 Hz, 1H), 3.52 (m, 4H), 2.16 (br m, 2H), 2.01 (m, 4H), 1.73 (br d, J = 7.6 Hz, 3H), 1.37 (br m, 2H), 1.26 (br m, 2H); ¹³C NMR (100 MHz, CDCl₃) ppm 173.7, 157.3, 153.8, 149.7, 143.4, 130.4, 128.3, 127.6, 127.0, 126.4, 124.6, 119.5, 118.8, 92.3, 67.7, 56.0, 53.4, 52.0, 33.4, 32.0, 25.8, 24.9, 24.8; HRMS (ESI): Exact mass calcd for C₃₉H₄₁N₄O [M+H]+ 581.3280, found 581.3264.

(3R,5R,7R)-N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl) adamantane-1-carboxamide (80l). To a flame dried flask equipped with a stir bar was added the amine (70.0 mg, 254 µmol) and dichloromethane (3 mL), immediately followed by the addition of N,N-diisopropyl ethylamine (53.0 µL, 305 µmol), the acid chloride (65.6 mg, 330 µmol), and DMAP (3.10 mg,
25.4 μmol). The reaction mixture was stirred at rt for 20 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO₃, extracted with dichloromethane, dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 10-40% ethyl acetate in hexanes) afforded the desired amide as an off white amorphous solid (96.5 mg, 87%). Mp 195.0-199.0 °C; [α]²⁰D +234 (c 0.65, CHCl₃); Rf = 0.33 (40% EtOAc/hexanes); IR (film) 3310, 3101, 3062, 2909, 2853, 1638, 1608, 1573, 1535 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.54 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.24 (ddd, J = 7.8, 7.8, 0.6 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 6.84 (s, 1H), 5.49 (d, J = 8.4 Hz, 1H), 4.26 (m, 1H), 3.72 (dddd, J = 10.8, 10.8, 7.2, 4.2 Hz, 1H), 2.15 (m, 2H), 1.84 (dd, J = 6.0, 2.4 Hz, 1H), 1.79 (ddd, J = 12.6, 2.4 Hz, 1H), 1.67 (br s, 3H), 1.45 (m, 12H), 1.32 (dq, J = 12.0, 3.0 Hz, 1H), 1.21 (br d, J = 12.0 Hz, 3H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 178.5, 157.0, 148.4, 142.5, 130.4, 126.1, 124.0, 122.5, 121.6, 112.6, 56.5, 52.8, 40.3, 38.8, 36.1, 32.9, 32.8, 27.9, 25.2, 24.7; HRMS (ESI) Exact mass calcd for C₂₆H₃₂ClN₃NaO [M+Na]⁺ 460.2132, found 460.2119.

(3R,5R,7R)-N-((1R,2R)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)adamantane-1-carboxamide (78l). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (50.0 mg, 114 µmol), pyrrolidine (37.5 µL, 457 µmol), and trifluorotoluene (820 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a tan solid (33.6 mg, 62%). Mp 239.0-243.0 °C; [α]²⁰D +139 (c 0.56, CHCl₃); Rf = 0.38 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3324, 2908, 2852, 1637, 1589, 1531 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.94 (dd, J = 8.4, 0.6 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.41 (ddd, J = 7.8, 7.8, 0.6 Hz, 1H), 7.34 (br d, J = 5.4 Hz, 1H), 7.04 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 5.63 (s, 1H), 4.34 (br s, 1H), 4.26 (m, 1H), 3.57
(dddd, \( J = 10.8, 10.8, 6.6, 4.2 \text{ Hz}, 1H \)) \( 3.51 \) (br s, \( 4H \)), \( 2.17 \) (d, \( J = 11.4 \) Hz, \( 1H \)), \( 2.05 \) (dd, \( J = 12.0, 1.8 \) Hz, \( 1H \)), \( 1.98 \) (m, \( 4H \)), \( 1.79 \) (dd, \( J = 13.2, 1.8 \) Hz, \( 1H \)), \( 1.73 \) (d, \( J = 12.0 \) Hz, \( 1H \)), \( 1.62 \) (s, \( 3H \)), \( 1.43 \) (m, \( 10H \)), \( 1.35 \) (m, \( 3H \)), \( 1.20 \) (d, \( J = 12.0 \) Hz, \( 3H \)); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 178.4, 158.2, 154.1, 149.6, 128.7, 126.6, 124.8, 119.8, 118.8, 92.1, 57.5, 52.0, 51.9, 40.2, 38.6, 36.2, 33.3, 32.7, 28.0, 25.7, 25.4, 24.6; HRMS (ESI): Exact mass calcd for C\(_{30}\)H\(_{40}\)N\(_4\)NaO \([\text{M+Na}^+]\) 495.3100, found 495.3089.

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\text{N-}((1R,2R)-2-((4-\text{Chloroquinolin-2-yl)amino)cyclohexyl)pivalamide} (80m).\]  
To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 \( \mu \)mol) and dichloromethane (3 mL), immediately followed by the addition of \( N,N \)-diisopropyl ethylamine (46.0 \( \mu \)L, 261 \( \mu \)mol), the acid chloride (32.0 \( \mu \)L, 261 \( \mu \)mol), and DMAP (2.70 mg, 22.0 \( \mu \)mol). The reaction mixture was stirred at rt for 24 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with satd aq NaHCO\(_3\), extracted with dichloromethane, dried (MgSO\(_4\)), filtered and concentrated. Flash column chromatography of the residue (SiO\(_2\), 20-50% ethyl acetate in hexanes) afforded the desired amide as a white solid (57.9 mg, 74%). Mp 213.0-216.0 \(^\circ\)C; \([\alpha]_{D}^{20}\) +281 (c 0.45, CHCl\(_3\)); \( R_f = 0.38 \) (40% EtOAc/hexanes); IR (film) 3313, 2932, 2858, 1607, 1576, 1535 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.96 (dd, \( J = 7.8, 0.6 \) Hz, \( 1H \)), 7.64 (d, \( J = 7.8 \) Hz, \( 1H \)), 7.56 (dd, \( J = 8.4, 6.6, 1.2 \) Hz, \( 1H \)), 7.27 (ddd, \( J = 7.8, 7.8, 1.2 \) Hz, \( 1H \)), 6.84 (d, \( J = 6.0 \) Hz, \( 1H \)), 6.71 (s, \( 1H \)), 5.03 (br d, \( J = 7.8 \) Hz, \( 1H \)), 4.18 (m, \( 1H \)), 3.71 (m, \( 1H \)), 2.16 (m, \( 2H \)), 1.82 (m, \( 1H \)), 1.78 (d, \( J = 10.8 \) Hz, \( 1H \)), 1.47-1.28 (m, \( 4H \)), 0.87 (s, \( 9H \)); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 179.1, 156.7, 148.3, 142.6, 130.5, 126.2, 124.0, 122.6, 121.6, 112.2, 56.1, 53.5, 38.4, 33.1, 32.5, 27.3, 25.1, 24.7; HRMS (ESI) Exact mass calcd for C\(_{20}\)H\(_{26}\)ClN\(_3\)NaO \([\text{M+Na}^+]\) 382.1662, found 382.1658.
**N-((1R,2R)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)pivalamide (78m).** A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (40.0 mg, 111 µmol), pyrrolidine (37.0 µL, 445 µmol), and trifluorotoluene (800 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a tan amorphous solid (23.5 mg, 54%). Mp 251.0-256.0 °C; [α]$_D^{20}$ +143 (c 0.69, CHCl₃); R$_f$ = 0.35 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3299, 2929, 2856, 2361, 1630, 1588, 1534 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl₃) δ 7.97 (d, $J$ = 7.8 Hz, 1H), 7.58 (br d, $J$ = 7.8 Hz, 1H), 7.47 (br s, 1H), 7.42 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.06 (dd, $J$ = 7.8, 7.8 Hz, 1H), 5.64 (s, 1H), 4.34 (br s, 1H), 4.21 (m, 1H), 3.60-3.54 (m, 5H), 2.22 (br d, $J$ = 11.4 Hz, 1H), 2.06 (br m, 1H), 1.99 (m, 4H), 1.80 (br d, $J$ = 10.8 Hz, 1H), 1.73 (br d, $J$ = 12.0 Hz, 1H), 1.46-1.28 (m, 4H), 0.84 (s, 9H); $^{13}$C NMR (150.9 MHz, CDCl₃) ppm 178.9, 158.1, 153.9, 149.6, 128.7, 126.6, 124.9, 119.8, 118.8, 92.0, 57.5, 52.3, 52.0, 38.3, 33.5, 32.4, 27.3, 25.8, 25.4, 24.6; HRMS (ESI) Exact mass calcd for C$_{24}$H$_{34}$N$_{4}$NaO [M+Na]$^+$ 417.2630, found 417.2630.

**2,2,2-Trichloro-N-((1R,2R)-2-((4-chloroquinolin-2-yl)amino)cyclohexyl)acetamide (80n).** To a flame dried flask equipped with a stir bar was added the amine (70.0 mg, 254 µmol) and dichloromethane (3 mL), immediately followed by the addition of N,N-diisopropyl ethylamine (53.0 µL, 305 µmol), the acid chloride (846 mg, 4.65 mmol), and DMAP (3.10 mg, 25.4 µmol). The reaction mixture was stirred at rt for 48 h, quenched with 1 M HCl and extracted with
dichloromethane. The organic extracts were then washed with satd aq NaHCO₃, extracted with dichloromethane, dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 5-40% ethyl acetate in hexanes) afforded the desired amide as a tan solid (76.3 mg, 71%). Mp 197.0-201.0 ºC; [α]D²⁰ +287 (c 0.47, CHCl₃); Rf = 0.27 (20% EtOAc/hexanes); IR (film) 3363, 2936, 2859, 1697, 1608, 1570, 1532 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.85 (br s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.57 (dd, J = 8.4, 7.8, 1.2 Hz, 1H), 7.30 (ddd, J = 7.8, 6.6, 0.6 Hz, 1H), 6.72 (s, 1H), 4.66 (br d, J = 7.2 Hz, 1H), 4.31 (dddd, J = 11.4, 11.4, 7.8, 4.2 Hz, 1H), 3.61 (m, 1H), 2.38 (br dd, J = 9.0, 5.4 Hz, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.83 (m, 1H), 1.48-1.41 (m, 4H), ¹³C NMR (150.9 MHz, CDCl₃) ppm 162.3, 156.5, 147.9, 143.2, 130.7, 126.4, 124.1, 123.2, 121.8, 112.0, 92.7, 60.2, 52.6, 33.0, 31.2, 25.2, 24.2; HRMS (ESI) Exact mass calcd for C₁₇H₁₈Cl₄N₃O [M+H]⁺ 420.0204, found 420.0222.

2,2,2-Trichloro-N-((1R,2R)-2-((4-(pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl) acetamide (78n). A 0.5-2 mL microwave vial was charged with the 4-chloroquinoline (30.0 mg, 71.0 µmol), pyrrolidine (24.0 µL, 285 µmol), and trifluorotoluene (525 µL). This suspension was heated at 150 ºC and stirred in the microwave for 90 min. The reaction was concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed three times more with 3 M aq NaOH. The combined organic layers were dried (MgSO₄) and concentrated to afford a yellow solid (9.3 mg, 29%). Mp 189.0-194.0 ºC; [α]D²⁰ +144 (c 0.64, CHCl₃); Rf = 0.42 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 3374, 2930, 1700, 1588, 1528 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.57 (br s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.58 (br d, J = 7.2 Hz, 1H), 7.42 (dd, J = 7.8, 7.8 Hz, 1H), 7.08 (dd, J = 7.8, 7.8 Hz, 1H), 5.65 (s, 1H), 4.28 (br s, 2H), 3.57 (br m, 4H), 3.51 (br s, 1H), 2.39 (br s, 1H), 2.06 (br d, J = 9.6 Hz, 1H), 2.00 (m, 4H), 1.85 (br d, J = 9.6 Hz, 1H), 1.80 (br d, J = 4.8 Hz, 1H), 1.47-1.37 (br m, 4H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 162.4, 157.9, 154.0, 149.2, 128.8, 126.8,
N-((1R,2R)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl) benzothioamide (78o). A flame dried flask equipped with a stir bar was charged with the amide (68.0 mg, 124 µmol) and toluene (3 mL) at room temperature. To the resulting solution was added Lawesson’s reagent (45.0 mg, 111 µmol) and the reaction mixture was heated to reflux and stirred. The reaction mixture was monitored by TLC; after 5 h, complete conversion was observed and the reaction mixture was concentrated. Flash column chromatography of the residue (SiO₂, 0.5-10% methanol in dichloromethane w/ 1% AcOH) afforded a yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried over MgSO₄ and concentrated to yield the desired thioamide as a yellow amorphous solid (32.0 mg, 46%). [α]_D^{20} +304 (c 0.53, CHCl₃); R_f = 0.19 (5% MeOH/1% AcOH/CH₂Cl₂); IR (film) 2930, 1588, 1527 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.93 (d, J = 7.8 Hz, 1H), 7.80 (s, 2H), 7.61 (s, 1H), 7.23 (dd, J = 7.2, 7.2 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.01 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 5.66 (s, 1H), 4.38 (d, J = 5.4 Hz, 1H), 4.30 (m, 1H), 4.16 (ddd, J = 14.4, 10.8, 3.6 Hz, 1H), 3.57 (m, 4H), 2.89 (d, J = 12.6 Hz, 1H), 2.08 (d, J = 13.2 Hz, 1H), 2.00 (m, 4H), 1.90 (br s, 1H), 1.85 (d, J = 9.0 Hz, 1H), 1.58-1.38 (m, 4H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 195.3, 158.0, 154.1, 148.2, 144.6, 131.1 (q, J = 33.3 Hz, 1C), 129.0, 126.8, 125.6, 124.9, 123.1 (q, J = 3.6 Hz), 122.8 (q, J = 273.0 Hz), 120.3, 118.5, 90.9, 65.7, 53.6, 52.0, 33.1, 29.1, 25.9, 25.5, 24.1; HRMS (ESI) Exact mass calcd for C₂₈H₂₉F₆N₄S [M+H]^+ 567.2018, found 567.2029.

**N-((1R,2R)-2-((4-Chloroquinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl) benzene sulfonamide (80p).** To a flame dried flask equipped with a stir bar was added the amine (60.0 mg, 218 µmol) and dichloromethane (3 mL), immediately followed by the addition of N,N-diisopropyl ethylamine (45.0 µL, 261 µmol), the sulfonyl chloride (82.0 mg, 261 µmol), and DMAP (2.70 mg, 22.0 µmol). The reaction mixture was stirred at rt for 25 h, quenched with 1 M HCl and extracted with dichloromethane. The organic extracts were then washed with NaHCO₃, extracted with dichloromethane, dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 5-30% ethyl acetate in hexanes) afforded the desired amide as a white solid (97.5 mg, 81%). Mp 206.0-208.0 °C; \([\alpha]_D^{20} +198 \text{ (c 0.58, CHCl}_3\text{)}; R_f = 0.64\) (40% EtOAc/hexanes); IR (film) 3379, 3065, 2937, 2862, 2361, 1609, 1535 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.31 (br s, 1H), 7.99 (dd, \(J = 8.4, 1.2 \text{ Hz, 1H}\)), 7.85 (s, 1H), 7.84 (s, 2H), 7.75 (d, \(J = 8.4 \text{ Hz, 1H}\)), 7.66 (ddd, \(J = 8.4, 7.2, 1.8 \text{ Hz, 1H}\)), 7.38 (ddd, \(J = 8.4, 7.2, 1.2 \text{ Hz, 1H}\)), 6.37 (s, 1H), 4.18 (br d, \(J = 4.8 \text{ Hz, 1H}\)), 3.81 (m, 1H), 2.99 (dt, \(J = 10.8, 4.2 \text{ Hz, 1H}\)), 2.37 (d, \(J = 10.2 \text{ Hz, 1H}\)), 1.98 (m, 1H), 1.78 (m, 2H), 1.59 (m, 1H), 1.38-1.30 (m, 3H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 156.0, 146.7, 144.0, 143.7, 132.0 (q, \(J_{FC} = 34.3 \text{ Hz}\)), 131.6, 126.7, 125.8, 125.2 (q, \(J_{FC} = 3.5 \text{ Hz}\)), 124.2, 124.0, 122.3 (q, \(J_{FC} = 273.3 \text{ Hz}\)), 121.7, 111.3, 62.4, 54.9, 35.2, 33.2, 24.7, 24.0; HRMS (ESI): Exact mass calcd for C₂₃H₂₁ClF₆N₃O₂S [M+H]⁺ 552.0947, found 552.0938.

**N-((1R,2R)-2-((4-(Pyrrolidin-1-yl)quinolin-2-yl)amino)cyclohexyl)-3,5-bis(trifluoromethyl) benzene sulfonamide (78p).** A 0.5-2 mL microwave vial was charged with 4-chloroquinoline (50.0 mg, 90.6 µmol), pyrrolidine (30.0 µL, 362 µmol), and trifluorotoluene (650 µL). This suspension was heated at 150 °C and stirred in the microwave for 90 min. The reaction was
concentrated and purified by flash column chromatography (1-10% methanol in dichloromethane w/ 1% AcOH) to provide a light yellow oil. This material was diluted with dichloromethane and washed with 6 M aq NaOH. The organic layers were combined and washed twice more with 3 M aq NaOH. The combined organic layers were dried (MgSO$_4$) and concentrated to afford an off-white solid (36.5 mg, 69%). Mp 238.0-240.0 °C; $[\alpha]^{20}_D +177$ (c 0.72, CHCl$_3$); R$_f$ = 0.53 (10% MeOH/1% AcOH/CH$_2$Cl$_2$); IR (film) 3378, 2931, 2361, 1586, 1534 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.03 (dd, J = 8.4, 0.6 Hz, 1H), 7.86 (s, 2H), 7.79 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.50 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 7.14 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 5.32 (s, 1H), 3.81 (br s, 1H), 3.69 (m, 1H), 3.56 (m, 4H), 2.77 (dt, J = 10.8, 4.2 Hz, 1H), 2.40 (br d, J = 13.2 Hz, 1H), 2.02 (m, 4H), 1.93 (br d, J = 11.4 Hz, 1H), 1.76 (m, 2H), 1.58 (m, 1H), 1.35-1.23 (m, 4H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 157.4, 154.1, 148.0, 143.8, 131.7 (q, $J_{CF} = 34.0$ Hz), 129.6, 127.1, 126.2, 125.0, 124.9 (q, J = 3.5 Hz), 122.5 (q, J = 273.3 Hz), 120.8, 118.3, 90.0, 62.3, 55.2, 51.9, 34.9, 33.3, 25.9, 24.9, 24.1; HRMS (ESI): Exact mass calcd for C$_{27}$H$_{29}$F$_6$N$_4$O$_2$S [M+H]$^+$ 587.1915, found 587.1893.

(Z)-tert-Butyl (2,2,2-trifluoro-1-phenylethylidene)carbamate (82).$^{256}$ To a flame dried flask equipped with a stir bar was added trifluoroacetophenone (1.22 mL, 8.69 mmol) and the iminophosphorane (3.61 g, 9.56 mmol). Toluene (35 mL) was added and the resulting solution was heated to reflux for 18 h. The reaction mixture was then cooled to room temperature, diluted with hexanes, and allowed to stir at rt for an additional 2 h whereupon a white solid precipitated out of solution. The mixture was then filtered with hexanes and the filtrate was concentrated. Flash column chromatography of the residue (SiO$_2$, 2-10% ethyl acetate in hexanes) afforded the desired ketimine as a clear colorless oil (1.46 g, 61%). R$_f$ = 0.54 (20% EtOAc/hexanes); IR (film) 3067, 2983, 2938, 1738, 1684 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.60 (br s, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 1.39 (s, 9H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 158.3, 154.1, 148.0, 143.8, 131.7 (q, $J_{CF} = 34.0$ Hz), 129.6, 127.1, 126.2, 125.0, 124.9 (q, J = 3.5 Hz), 122.5 (q, J = 273.3 Hz), 120.8, 118.3, 90.0, 62.3, 55.2, 51.9, 34.9, 33.3, 25.9, 24.9, 24.1; HRMS (ESI) Exact mass calcd for C$_{13}$H$_{18}$F$_3$NO$_2$ [M+H]$^+$ 274.1055, found decomposition upon submission.

(R)-tert-Butyl (1,1,1-trifluoro-3-nitro-2-phenylpropan-2-yl)carbamate (87). To a flame dried vial equipped with a stir bar was added PBAM·HNTf₂ (11.5 mg, 14.6 µmol), toluene (293 µL) and nitromethane (79.0 µL, 1.46 mmol). The resulting mixture was chilled to -20 °C before addition of the ketimine (20.0 mg, 73.2 µmol). The reaction stirred at -20 °C for 5 days. The reaction was directly filtered through a pad of silica gel with CH₂Cl₂ and EtOAc and the filtrate was concentrated. Flash column chromatography of the residue (SiO₂, 1-10% ethyl acetate in hexanes) afforded the desired adduct as a white crystalline solid (8.40 mg, 34%) that was found to be 66% ee by chiral HPLC; (Chiralpak AD, 5% iPrOH/hexanes, 1 mL/min, tᵣ(major) 12.7 min, tᵣ(minor) 11.2 min); Mp 80.0-82.0 °C; [α]D₂₀ +13.9 (c 0.49, CHCl₃); Rᵣ = 0.43 (20% EtOAc/hexanes); IR (film) 3259, 3159, 2979, 2361, 1717, 1563, 1502 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.44 (s, 5H), 5.55 (br d, J = 12.0 Hz, 1H), 5.48 (br d, J = 12.0 Hz, 1H), 5.42 (s, 1H), 1.46 (s, 9H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 153.6, 132.6, 129.7, 129.0, 126.1, 123.9 (q, J_CF = 286.0 Hz), 81.8, 73.1, 63.9 (q, J_CF = 28.1 Hz), 28.1; HRMS (ESI): Exact mass calcd for C₁₄H₁₇F₃N₂NaO₄ [M+Na]⁺ 357.1038, found 357.1040.

(R)-tert-Butyl (3-amino-1,1,1-trifluoro-2-phenylpropan-2-yl)carbamate (90). The nitroalkane (192 mg, 574 µmol) was dissolved in MeOH (2.3 mL) at rt. CoCl₂ (74.5 mg, 574 µmol) was added and the reaction mixture was chilled to 0 °C before NaBH₄ (327 mg, 8.62 mmol) was added in three portions over 40 min. The reaction mixture was warmed to rt and allowed to stir for an additional 2 h before being quenched with 1 M HCl. The reaction mixture was adjusted to pH 10 with conc aq NH₄OH. The solution was then filtered through a glass frit with water and CH₂Cl₂ and the layers were separated. The organic layer was dried (MgSO₄) and concentrated to afford the amine as an off-white crystalline solid (150 mg, 86%) which was determined to be 69% ee by chiral HPLC analysis (Chiralcel OJ, 10% iPrOH/hexanes, 1 mL/min tᵣ(major) = 10.8 min, tᵣ(minor) = 6.2 min). Mp 77.0-79.0 °C; Rᵣ = 0.47 (5% MeOH/1%AcOH/CH₂Cl₂); IR (film) 3328, 2978, 1719 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.44 (d, J = 8.4 Hz, 2H), 7.38 (dd, J = 7.2, 7.2 Hz, 2H), 1.46 (s, 9H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 141.6, 129.7, 129.0, 126.1, 123.9 (q, J_CF = 286.0 Hz), 81.8, 73.1, 63.9 (q, J_CF = 28.1 Hz), 28.1; HRMS (ESI): Exact mass calcd for C₁₄H₁₇F₃N₂NaO₄ [M+Na]⁺ 357.1038, found 357.1040.
7.34 (m, 1H), 5.67 (br s, 1H), 3.65 (br d, J = 11.4 Hz, 1H), 3.26 (br d, J = 8.4 Hz, 1H), 1.39 (br s, 9H), 1.26 (br s, 2H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 154.0, 128.5, 128.3, 126.3, 126.0 (q, J = 287 Hz), 80.5, 65.1 (q, J = 25.7 Hz), 46.7, 29.7, 28.1; HRMS (EI) Exact mass calcd for C$_{15}$H$_{19}$ClN$_3$ [M+] 304.1399, found 304.1393.

tert-Butyl (1,1,1-trifluoro-3-(2-isoproxy-4-methoxybenzamido)-2-phenylpropan-2-yl)carbamate (92). To a flame dried flask equipped with a stir bar was added the amine (231 mg, 759 µmol), the carboxylic acid (159 mg, 759 µmol), and dichloromethane (4 mL). The resulting solution was chilled to 0 °C and EDC (189 mg, 987 µmol) and DMAP (9.30 mg, 76.0 µmol) were added. The reaction mixture was stirred and allowed to gradually warm to room temperature. After 16 h, the reaction mixture was diluted with water and extracted with CH$_2$Cl$_2$. The combined organic layers were washed once with water, dried (MgSO$_4$), and concentrated. Flash column chromatography of the residue (SiO$_2$, 10-40% ethyl acetate in hexanes) afforded the desired amide as a white foam (367 mg, 97%). R$_f$ = 0.77 (5% MeOH/1%AcOH/CH$_2$Cl$_2$); IR (film) 3388, 3281, 2979, 1734, 1643, 1605, 1532 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.39 (dd, J = 6.0, 6.0 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.38 (dd, J = 7.2, 7.2 Hz, 2H), 7.33 (dd, J = 7.2, 7.2 Hz, 1H), 6.58 (dd, J = 9.0, 2.4 Hz, 1H), 6.45 (d, J = 1.8 Hz, 1H), 6.42 (br s, 1H), 4.65 (qq, J = 6.0, 6.0 Hz, 1H), 4.21 (br dd, J = 12.6, 5.4 Hz, 1H), 4.03 (dd, J = 14.4, 5.6 Hz, 1H), 3.83 (s, 3H), 1.39 (br s, 9H), 1.33 (d, J = 6.6 Hz, 3H), 1.27-1.24 (m, 3H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 166.9, 163.6, 157.3, 153.9, 135.2, 134.3, 128.4, 128.2, 126.3, 125.7 (q, J = 288 Hz), 114.3, 105.2, 100.2, 80.3, 71.6, 66.4 (q, J = 25.8 Hz), 55.5, 45.5, 28.1, 21.7, 21.6; HRMS (ESI) Exact mass calcd for C$_{25}$H$_{31}$F$_3$N$_2$NaO$_5$ [M+Na]$^+$ 519.2083, found 519.2067.

$N$-(2-Amino-3,3,3-trifluoro-2-phenylpropyl)-2-isoproxy-4-methoxybenzamide (93). The amide (367 mg, 739 µmol) was dissolved in CH$_2$Cl$_2$ (8 mL), treated with TFA (2.27 mL, 29.6 mmol), and stirred at rt for 16 h. The reaction mixture was poured into satd aq NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The combined organic layers were dried (MgSO$_4$), filtered, and
concentrated to afford the amine as a light orange solid (293 mg, 100%). Mp 87.0-90.0 °C; \(R_f = 0.65\) (5% MeOH/1% AcOH/CH\(_2\)Cl\(_2\)); IR (film) 3384, 2980, 1645, 1605, 1531 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.16 (d, \(J = 9.0\) Hz, 1H), 8.11 (dd, \(J = 5.4\) Hz, 1H), 7.64 (d, \(J = 7.8\) Hz, 2H), 7.40 (m, 2H), 7.35 (dt, \(J = 5.4, 1.2\) Hz, 1H), 6.54 (dd, \(J = 8.4, 2.4\) Hz, 1H), 6.38 (d, \(J = 2.4\) Hz, 1H), 4.55 (qq, \(J = 6.0, 6.0\) Hz, 1H), 4.20 (dd, \(J = 13.8, 6.0\) Hz, 1H), 4.14 (dd, \(J = 13.8, 6.0\) Hz, 1H), 3.80 (s, 3H), 1.97 (br s, 2H), 1.14 (d, \(J = 6.0\) Hz, 3H), 1.13 (d, \(J = 6.0\) Hz, 3H); \(^{13}\)C NMR (150.9 MHz, CDCl\(_3\)) ppm 166.1, 163.3, 157.2, 136.1, 134.2, 128.6, 128.5, 127.0, 126.5 (q, \(J = 286\) Hz), 114.5, 105.1, 100.2, 71.4, 62.1 (q, \(J = 24.1\) Hz), 55.4, 43.8, 21.59, 21.55; HRMS (ESI) Exact mass calcd for C\(_{20}\)H\(_{24}\)F\(_3\)N\(_2\)O\(_3\) [M+H]\(^+\) 397.1715, found 397.1725.

2-Isoproxy-4-methoxy-N-(3,3,3-trifluoro-2-phenyl-2-(3-phenylureido)propyl)benzamide (99). To a vial equipped with a stir bar was added the amine (40.0 mg, 101 µmol) and isocyanate (331 µL, 3.03 mmol). The resulting mixture was stirred at rt 24 h, diluted with dichloromethane and washed with satd aq NaHCO\(_3\). The aqueous layer was extracted with dichloromethane and the organic extracts were dried (MgSO\(_4\)), filtered and concentrated. Flash column chromatography of the residue (SiO\(_2\), 5-100% diethyl ether in hexanes) afforded the desired urea as an off-white viscous oil (47.4 mg, 91%). \(R_f = 0.46\) (40% EtOAc/hexanes); IR (film) 3349, 3062, 2980, 2361, 1712, 1626, 1603, 1553 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.61 (dd, \(J = 6.4, 6.4\) Hz, 1H), 8.11 (dd, \(J = 7.6\) Hz, 2H), 7.38-7.31 (m, 3H), 7.26 (dd, \(J = 8.4, 8.4\) Hz, 3H), 7.18 (dd, \(J = 7.6, 7.6\) Hz, 2H), 7.07 (br s, 1H), 6.96 (dd, \(J = 7.2, 7.2\) Hz, 1H), 6.53 (dd, \(J = 8.8, 2.0\) Hz, 1H), 6.42 (br d, \(J = 2.0\) Hz, 1H), 4.63 (qq, \(J = 6.4, 6.4\) Hz, 1H), 4.18 (br dd, \(J = 14.0, 6.8\) Hz, 1H), 4.04 (dd, \(J = 14.4, 6.0\) Hz, 1H), 3.83 (s, 3H), 1.30 (d, \(J = 6.0\) Hz, 3H), 1.26 (d, \(J = 6.0\) Hz, 3H); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) ppm 167.8, 163.8, 157.6, 153.7, 138.7, 135.4, 134.1, 128.8, 128.6, 128.3, 126.2, 125.9 (q, \(J = 288.6\) Hz), 123.0, 119.7, 113.7, 105.3, 100.3, 71.9, 67.2 (q, \(J = 25.9\) Hz), 55.5, 46.8, 21.63, 21.61; HRMS (ESI) Exact mass calcd for C\(_{27}\)H\(_{27}\)F\(_3\)N\(_3\)O\(_4\) [M+H]\(^+\) 516.2110, found 516.2094.
2-Isoproxy-4-methoxy-N-(3,3,3-trifluoro-2-(3-(4-nitrophenyl)ureido)-2-phenylpropyl) benzamide (102). To a vial equipped with a stir bar was added the amine (40.0 mg, 101 µmol) and isocyanate (166 mg, 1.01 mmol). Benzene (1 mL) was added and the resulting mixture was stirred at rt 72 h. The solution was then diluted with dichloromethane and washed with satd aq NaHCO₃. The aqueous layer was extracted with dichloromethane and the organic extracts were dried (MgSO₄), filtered and concentrated. Flash column chromatography of the residue (SiO₂, 50-100% diethyl ether in hexanes) afforded the desired urea as a light yellow viscous oil (30.4 mg, 55%). Rf = 0.23 (100% diethyl ether); IR (film) 3352, 3094, 2928, 1722, 1626, 1603, 1555, 1501 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.72 (dd, J = 6.0, 6.0 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 8.04 (d, J = 9.0 Hz, 2H), 7.84 (br s, 1H), 7.77 (s, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.46-7.41 (m, 4H), 7.37 (m, 1H), 6.52 (dd, J = 8.4, 1.8 Hz, 1H), 6.42 (d, J = 1.8 Hz, 1H), 4.67 (qq, J = 6.0, 6.0 Hz, 1H), 4.10 (dd, J = 14.4, 7.2 Hz, 1H), 3.94 (dd, J = 15.0, 6.0 Hz, 1H), 3.83 (s, 3H), 1.33 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 168.7, 164.2, 157.7, 152.5, 145.3, 142.2, 134.8, 133.9, 128.9, 128.6, 125.8, 125.8 (q, J = 289.3 Hz), 125.0, 117.8, 112.9, 105.6, 100.2, 72.0, 67.7 (q, J = 26.4 Hz), 55.6, 48.0, 21.72, 21.69; HRMS (ESI) Exact mass calcd for C₂₇H₂₈F₃N₄O₆ [M+H]⁺ 561.1961, found 561.1944.

General procedure for Hypervalent Iodine-Mediated Intermolecular Diamination: A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL) and was chilled to 0 °C. The amine (900 µmol) and vinylphenol (300 µmol) were added and the resulting mixture was stirred at 0 °C for 18
h. The reaction mixture was then diluted with ethyl acetate and concentrated. No reductive workup was used in these studies, but is recommended for a larger scale.

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\begin{align*}
\text{2-(1,2-Dithiomorpholinoethyl)phenol (338a). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO}_2, 5-60\% \text{ diethyl ether in hexanes) afforded the desired product as a light orange amorphous solid (97.0 mg, 99\%). Mp 82.0-86.0 °C; R_f = 0.06 (10\% EtOAc/hexanes); IR (film) 3040 (br), 2910, 2810, 1607, 1587 cm}^{-1}; \text{1H NMR (600 MHz, CDCl}_3) \delta 11.18 (br s, 1H), 7.15 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 7.02 (dd, J = 7.8, 0.6 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.79 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 3.77 (dd, J = 6.6, 6.6 Hz, 1H), 3.10 (dd, J = 7.2, 3.0 Hz, 1H), 3.08 (dd, J = 6.6, 3.0 Hz, 1H), 2.92-2.88 (m, 3H), 2.77-2.65 (m, 9H), 2.64-2.61 (m, 4H); \text{13C NMR (150 MHz, CDCl}_3) \text{ppm} 157.3, 128.7, 128.4, 124.8, 119.1, 116.7, 65.6, 59.2, 55.6, 52.2, 28.04, 27.97; \text{HRMS (ESI): Exact mass calcd for C}_{16}H_{25}N_{2}O_{2} [M+H]^+ 325.1408, found 325.1395.}
\end{align*}
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\begin{align*}
\text{4-(1,2-Dithiomorpholinoethyl)phenol (340a). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 4-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO}_2, 25-50-75-100\% \text{ diethyl ether in hexanes) afforded the desired product as a light brown solid (60.4 mg, 62\%). Mp 139.0-143.0 °C; R_f = 0.21 (80\% EtOAc/hexanes); IR (film) 3200 (br), 2916, 2815, 1611, 1513 cm}^{-1}; \text{1H NMR (400 MHz, CDCl}_3) \delta 7.74 (br s, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 3.69 (dd, J = 6.4, 6.4 Hz, 1H), 2.97 (dd, J = 13.2, 6.4 Hz, 1H), 2.91-2.86 (m, 2H), 2.80-2.71 (m, 7H), 2.66-2.58 (m, 8H); \text{13C NMR (125 MHz, CDCl}_3) \text{ppm} 155.6, 129.7, 129.1, 115.1, 111.9, 66.6, 60.6, 55.3, 52.1, 27.9, 27.4; \text{HRMS (ESI): Exact mass calcd for C}_{16}H_{25}N_{2}O_{2} [M+H]^+ 325.1408, found 325.1411.}
\end{align*}
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2-(1,2-Dimorpholinoethyl)phenol (338b). Prepared according to the general procedure using morpholine (78.0 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 10-100% diethyl ether in hexanes) afforded the desired product as an off-white solid (69.2 mg, 79%). Mp 86.0-89.0 °C; R<sub>f</sub> = 0.27 (100% Et₂O); IR (film) 3040 (br), 2958, 2851, 1588 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.60 (br s, 1H), 7.15 (dd, <i>J</i> = 7.6, 7.6 Hz, 1H), 6.99 (d, <i>J</i> = 7.6 Hz, 1H), 6.79 (d, <i>J</i> = 8.0 Hz, 1H), 6.78 (dd, <i>J</i> = 8.0, 8.0 Hz, 1H), 3.79-3.69 (m, 4H), 3.64 (dd, <i>J</i> = 4.0 Hz, 4H), 3.54 (dd, <i>J</i> = 5.6, 5.6 Hz, 1H); 2.94 (dd, <i>J</i> = 13.6, 6.4 Hz, 1H), 2.81-2.74 (br m, 2H), 2.63-2.56 (m, 3H), 2.49-2.36 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) ppm 156.7, 129.1, 128.7, 124.8, 119.2, 116.6, 67.3, 67.0, 66.9, 60.4, 54.2, 51.6; HRMS (ESI): Exact mass calcd for C<sub>16</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 293.1865, found 293.1852.

2-(1,2-Di(piperidin-1-yl)ethyl)phenol (338c). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (290 mg, 900 µmol), and acetonitrile (3 mL) and was chilled to 0 °C. Piperidine (89.0 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at 0 °C for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 50-100% diethyl ether in hexanes) afforded the desired product as a light brown solid (25.4 mg, 29%). Mp 59.0-62.0 °C; R<sub>f</sub> = 0.11 (20% EtOAc/hexanes); IR (film) 3050 (br), 2933, 2851, 1588 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.17 (br s, 1H), 7.13 (ddd, <i>J</i> = 7.6, 7.6, 1.6 Hz, 1H), 7.08 (dd, <i>J</i> = 7.6, 1.2 Hz, 1H), 6.80 (dd, <i>J</i> = 8.0, 1.2 Hz, 1H), 6.76 (dd, <i>J</i> = 7.6, 7.6, 1.2 Hz, 1H), 3.77 (dd, <i>J</i> = 6.0, 6.0 Hz, 1H), 2.93 (dd, <i>J</i> = 13.6, 5.6 Hz, 1H), 2.79-2.72 (m, 2H), 2.62 (dd, <i>J</i> = 13.2, 6.0 Hz, 1H), 2.61-2.54 (m, 2H), 2.51-2.39 (m, 4H), 1.70-1.52 (m, 8H), 1.51-1.45 (m, 2H), 1.45-1.36 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) ppm 157.9, 128.4, 128.2, 126.2, 118.6, 116.6,
2-(1,2-Di(isoindolin-2-yl)ethyl)phenol (338d). Prepared according to the general procedure using isoindoline (102 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 5-100% diethyl ether in hexanes) afforded the desired product as a dark-brown viscous oil (31.9 mg, 30%). R_f = 0.68 (40% EtOAc/hexanes); IR (film) 3047, 2937, 2797, 1690, 1588 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.15 (m, 9H), 7.12 (dd, J = 7.6, 1.6 Hz, 1H), 6.88 (dd, J = 8.0, 0.8 Hz, 1H), 6.83 (dd, J = 7.2, 7.2, 0.8 Hz, 1H), 4.11 (s, 4H), 4.03-3.94 (m, 4H), 4.00 (dd, J = 6.0, 6.0 Hz, 1H), 3.47 (dd, J = 13.2, 6.0 Hz, 1H), 3.16 (dd, J = 13.2, 6.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) ppm 156.9, 139.7, 139.0, 129.0, 128.9, 127.0, 126.8, 125.9, 122.3, 122.2, 119.3, 116.7, 69.3, 60.2, 60.1, 57.9; HRMS (ESI): Exact mass calcd for C₂₄H₂₅N₂O [M+H]⁺ 357.1967, found 357.1968.

Dibenzyl 4,4’-(1-(2-hydroxyphenyl)ethane-1,2-diyl)bis(piperazine-1-carboxylate) (338e). Prepared according to the general procedure using benzyl piperazine-1-carboxylate (174 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 5-80% ethyl acetate in hexanes) afforded the desired product as a yellow viscous oil (105 mg, 62%). R_f = 0.04 (20% EtOAc/hexanes); IR (film) 3033, 2940, 2897, 2859, 2823, 1702, 1588 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.79 (br s, 1H); 7.39-7.28 (m, 10H), 7.16 (dd, J = 8.4, 8.4, 1.6 Hz, 1H), 6.97 (dd, J = 7.6, 1.6 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.78 (dd, J = 7.2, 7.2, 1.2 Hz, 1H), 5.13 (s, 2H), 5.12 (s, 2H), 3.62-3.42 (m, 9H), 2.95 (dd, J = 13.6, 6.4 Hz, 1H), 2.75 (br s, 2H), 2.59 (dd, J = 13.6, 5.2 Hz, 1H), 2.63-2.52 (m, 2H), 2.50-2.27 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) ppm 156.7, 155.1, 155.0, 136.6, 136.5, 128.83, 128.81, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, ,
124.7, 119.3, 116.7, 67.2, 67.1, 66.8, 59.9, 53.4, 50.6, 43.7; HRMS (ESI): Exact mass calcd for C_{32}H_{39}N_{4}O_{5} [M+H]^+ 559.2920, found 559.2897.

**Di-tert-butyl 4,4'-(1-(2-hydroxyphenyl)ethane-1,2-diyl)bis(piperazine-1-carboxylate) (338f).**
Prepared according to the general procedure using tert-butyl piperazine-1-carboxylate (117 mg, 630 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 20-80% ethyl acetate in hexanes) afforded the desired product as a light-yellow non-viscous oil (86.4 mg, 59%). R_f = 0.10 (20% EtOAc/hexanes); IR (film) 3040 (br), 2975, 2929, 2857, 1697, 1589 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.00 (br s, 1H), 7.14 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 6.98 (dd, J = 7.6, 0.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.77 (dd, J = 8.0, 8.0 Hz, 1H), 3.57 (dd, J = 6.0, 6.0 Hz, 1H), 3.53-3.40 (m, 4H), 3.39-3.32 (m, 4H), 2.95 (dd, J = 13.6, 6.4 Hz, 1H), 2.78-2.68 (br m, 2H), 2.57 (dd, J = 13.2, 5.2 Hz, 1H), 2.61-2.51 (m, 2H), 2.48-2.28 (m, 4H), 1.45 (s, 9H), 1.44 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) ppm 156.8, 154.7, 154.5, 128.8, 128.7, 125.0, 119.3, 116.7, 79.9, 79.6, 66.9, 60.0, 53.5, 50.7, 44.0, 43.2, 28.4; HRMS (ESI): Exact mass calcd for C_{26}H_{43}N_{4}O_{5} [M+H]^+ 491.3234, found 491.3233.

**Diethyl 4,4'-(1-(2-hydroxyphenyl)ethane-1,2-diyl)bis(piperazine-1-carboxylate) (338g).**
Prepared according to the general procedure using ethyl 1-piperazinecarboxylate (132 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 10-80% ethyl acetate in hexanes) afforded the desired product as a viscous transparent yellow oil (117 mg, 90%). R_f = 0.22 (40% EtOAc/hexanes); IR (film) 3000 (br), 2982, 2860, 1699, 1589 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.39 (br s, 1H), 7.13 (ddd, J = 8.8, 1.6 Hz, 1H), 6.97 (dd, J = 7.2, 1.2 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.77 (ddd, J = 8.4, 0.8 Hz, 1H), 4.11 (dq, J = 6.8, 6.8 Hz, 4H), 3.57 (dd, J = 5.6, 5.6 Hz, 1H), 3.54-3.43 (m, 4H), 3.42-3.35 (m, 4H), 2.94 (dd, J = 13.6, 6.4 Hz, 1H), 2.78-2.69 (m, 2H), 2.60-2.52 (m, 3H), 2.45-2.30 (m, 4H), 1.25-1.21 (m, 6H); ¹³C
NMR (125 MHz, CDCl₃) ppm 156.7, 155.4, 155.2, 128.8, 124.8, 119.3, 116.7, 66.8, 61.5, 61.3, 60.0, 53.4, 50.6, 43.6, 14.6; HRMS (ESI): Exact mass calcd for C₂₂H₃₅N₄O₅ [M+H]+ 435.2607 found 435.2599.

2-(1,2-Bis(4-phenylpiperazin-1-yl)ethyl)phenol (338h). Prepared according to the general procedure using 1-phenylpiperazine (137 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 5-100% diethyl ether in hexanes) afforded the desired product as an off-white solid (41.7 mg, 31%). Mp 179.0-182.0 °C; Rᶠ = 0.57 (100% Et₂O); IR (film) 3038, 2946, 2881, 2823, 1600 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.29 (br s, 1H), 7.32-7.27 (m, 4H), 7.20 (ddd, J = 9.2, 9.2, 1.6 Hz, 1H), 7.09 (dd, J = 7.6, 1.2 Hz, 1H), 6.94 (dd, J = 7.6, 3.6 Hz, 4H), 6.91-6.82 (m, 4H), 3.68 (dd, J = 6.0, 6.0 Hz, 1H), 3.34-3.28 (m, 2H), 3.26-3.22 (m, 2H), 3.19 (dd, J = 5.2, 5.2 Hz, 4H), 3.10 (dd, J = 13.6, 6.4 Hz, 1H), 3.04-2.99 (m, 2H), 2.83 (ddd, J = 10.4, 6.4, 2.8 Hz, 2H), 2.72-2.68 (m, 3H), 2.65-2.60 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) ppm 157.0, 151.2, 150.9, 129.2, 129.1, 129.0, 128.7, 125.3, 120.1, 119.7, 119.2, 116.7, 116.2, 116.0, 66.9, 60.1, 53.8, 50.9, 49.4, 49.2; HRMS (ESI): Exact mass calcd for C₂₈H₃₅N₄O [M+H]+ 443.2811, found 443.2802.

2-(1,2-Bis(4-(3-methoxyphenyl)piperazin-1-yl)ethyl)phenol (338i). Prepared according to the general procedure using 1-(3-methoxyphenyl)piperazine (155 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 20% ethyl acetate in hexanes) afforded the desired product as a light-brown viscous oil (23.4 mg, 16%). Rᶠ = 0.15 (20% EtOAc/hexanes); IR (film) 2938, 2829, 1602, 1494 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 11.15 (br s, 1H), 7.19-7.15 (m, 3H), 7.05 (dd, J = 7.2, 1.2 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.81 (ddd, J =
7.8, 7.8, 1.2 Hz, 1H), 6.52 (ddd, J = 7.2, 4.2, 1.8 Hz, 2H), 6.47-6.40 (m, 4H), 3.79 (s, 3H), 3.79 (s, 3H), 3.66 (dd, J = 6.0, 6.0 Hz, 1H), 3.30-3.24 (m, 2H), 3.22-3.12 (m, 6H), 3.06 (dd, J = 13.2, 6.6 Hz, 1H), 3.00-2.94 (m, 2H), 2.81-2.76 (m, 2H), 2.68-2.62 (m, 3H), 2.61-2.55 (m, 2H); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) ppm 160.6, 160.5, 156.9, 152.6, 152.3, 129.8, 129.7, 129.0, 128.7, 125.2, 119.2, 116.7, 108.9, 108.8, 104.8, 104.5, 102.6, 102.5, 66.9, 60.1, 55.2, 53.7, 50.9, 49.3, 49.1; HRMS (ESI): Exact mass calcd for C\textsubscript{30}H\textsubscript{39}N\textsubscript{4}O\textsubscript{3} [M+H\textsuperscript{+}] 503.3022, found 503.3006.

2-(1,2-bis(4-cinnamylpiperazin-1-yl)ethyl)phenol (338j). Prepared according to the general procedure using trans-1-cinnamylpiperazine (182 mg, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO\textsubscript{2}, 0.5-1-2-5-10% methanol in dichloromethane) afforded the desired product as a light-brown viscous oil (146.8 mg, 94%). R\textsubscript{f} = 0.29 (5% MeOH/DCM); IR (film) 3385 (br), 3026, 2937, 2811, 1588 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) \textdelta 7.92 (br s, 1H), 7.38-7.36 (m, 4H), 7.31 (dd, J = 7.2 Hz, 4H), 7.26-7.23 (m, 2H), 7.14 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 6.99 (dd, J = 7.8, 1.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 7.2, 7.2 Hz, 1H), 6.54 (dd, J = 16.2, 8.4 Hz, 2H), 6.23-6.24 (m, 2H), 3.59 (dd, J = 5.4, 5.4 Hz, 1H), 3.27 (d, J = 6.6 Hz, 2H), 3.22 (ddddd, J = 6.6, 6.6, 6.6, 6.6 Hz, 2H), 2.95 (dd, J = 13.8, 6.0 Hz, 1H), 3.10-2.40 (m, 17H); \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) ppm 157.0, 136.5, 136.3, 134.9, 134.2, 128.9, 128.7, 128.59, 128.57, 127.9, 127.7, 126.5, 126.4, 125.0, 124.9, 123.8, 119.1, 116.6, 66.7, 60.6, 60.4, 59.3, 53.0, 52.7, 52.6, 50.0; HRMS (ESI): Exact mass calcd for C\textsubscript{34}H\textsubscript{43}N\textsubscript{4}O [M+H\textsuperscript{+}] 523.3437, found 523.3416.
2-(1,2-Bis(dibenzylamino)ethyl)phenol (338k). Prepared according to the general procedure using dibenzylamine (173 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 0.25-0.5-1-2% ethyl acetate in hexanes) afforded the desired product as a light-yellow viscous oil (53.1 mg, 35%). R_f = 0.84 (40% EtOAc/hexanes); IR (film) 3061, 3028, 2835, 1585, 1493 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.77 (br s, 1H), 7.30-7.18 (m, 16H), 7.16-7.12 (m, 6H), 6.82 (dd, J = 8.4, 1.2 Hz, 1H), 6.76 (ddd, J = 7.6, 1.2 Hz, 1H), 4.10 (dd, J = 8.8, 4.0 Hz, 1H), 3.62 (s, 2H), 3.62 (s, 2H), 3.52 (d, J = 13.2 Hz, 2H), 3.41 (d, J = 13.2 Hz, 2H), 3.11 (dd, J = 13.2, 4.0 Hz, 1H), 2.97 (dd, J = 13.2, 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) ppm 157.0, 138.6, 137.7, 129.4, 129.2, 128.6, 128.5, 128.2, 127.4, 127.1, 125.6, 119.0, 116.6, 61.3, 59.1, 54.1, 52.5; HRMS (ESI): Exact mass calcd for C₃₆H₃₇N₂O [M+H]⁺ 513.2906, found 513.2894.

2-(1,2-Bis(benzyl(methyl)amino)ethyl)phenol (338l). Prepared according to the general procedure using N-benzylmethylamine (116 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a light-yellow transparent viscous oil (70.0 mg, 65%). R_f = 0.43 (30% EtOAc/hexanes); IR (film) 3061, 3028, 2948, 2844, 2791, 1587 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.35-7.23 (m, 10H), 7.19 (ddd, J = 9.0, 9.0, 1.2 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.83 (dd, J = 7.2, 7.2 Hz, 1H), 3.89 (dd, J = 6.0, 6.0 Hz, 1H), 3.78 (d, J = 13.2 Hz, 1H), 3.69 (d, J = 12.6 Hz, 1H), 3.59 (d, J = 13.2 Hz, 1H), 3.52 (d, J = 13.2 Hz, 1H), 3.11 (dd, J = 13.2, 5.4 Hz, 1H), 2.83 (13.2, 6.0 Hz, 1H), 2.24 (s, 3H), 2.22 (s, 3H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 157.3, 138.6, 137.6, 129.2, 129.0, 128.6, 128.51, 128.45, 128.3, 127.4, 127.1, 126.0, 119.0, 116.7, 65.9, 63.1, 59.0, 58.2, 42.6, 38.0; HRMS (ESI): Exact mass calcd for C₂₄H₂₉N₂O [M+H]⁺ 361.2280, found 361.2288.
2-(1,2-Bis(phenylamino)ethyl)phenol (338m). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). Aniline (82.0 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 2-5-10-20% ethyl acetate in hexanes) afforded the desired product as a brown viscous oil (54.6 mg, 60%). R<sub>f</sub> = 0.26 (10% EtOAc/hexanes); IR (film) 3391, 3050, 1602, 1499 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 9.69 (br s, 1H), 7.25-7.20 (m, 4H), 7.16 (dd, <i>J</i> = 8.4, 7.6 Hz, 2H), 6.94 (dd, <i>J</i> = 7.2, 7.2, 0.8 Hz, 1H), 6.91-6.78 (m, 5H), 6.74 (d, <i>J</i> = 7.6 Hz, 2H), 4.70 (br s, 1H), 4.53 (dd, <i>J</i> = 9.6, 4.8 Hz, 1H), 3.91 (br s, 1H), 3.63 (dd, <i>J</i> = 13.2, 9.6 Hz, 1H), 3.51 (dd, <i>J</i> = 13.2, 4.4 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl₃) ppm 156.7, 147.4, 146.7, 129.5, 129.3, 129.1, 128.0, 124.2, 121.2, 120.3, 118.9, 117.3, 116.7, 113.7, 60.2, 49.1; HRMS (ESI): Exact mass calcd for C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O [M+H]<sup>+</sup> 305.1648, found 305.1643.

2-(1,2-Bis((4-(tert-butyl)phenyl)amino)ethyl)phenol (338n). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). The aniline (143 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-1-2-5-10% ethyl acetate in hexanes) afforded the desired product as a brown viscous oil (66.5 mg, 53%). R<sub>f</sub> = 0.49 (20% EtOAc/hexanes); IR (film) 3307, 3049, 2961, 2903, 2866, 1614, 1588, 1518 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 10.06 (br s, 1H), 7.26-7.16 (m, 6H), 6.92 (dd, <i>J</i> = 7.2, 7.2, 1.2 Hz, 1H), 6.84 (d, <i>J</i> = 8.0 Hz, 1H), 6.74 (d, <i>J</i> = 8.4 Hz, 2H), 6.69 (d, <i>J</i> = 8.8 Hz, 2H), 4.69 (br s, 1H), 4.47 (dd, <i>J</i> = 9.6, 4.4 Hz, 1H), 3.81 (br s, 1H), 3.61 (dd, <i>J</i> = 13.2, 10.8 Hz, 1H), 3.47
2-(1,2-Bis((3,5-dimethylphenyl)amino)ethyl)phenol (338o). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). The aniline (112 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 2-5-10-20% ethyl acetate in hexanes) afforded the desired product as a light brown solid (64.3 mg, 60%). Mp 120.0-124.0 °C; R$_f$ = 0.44 (20% EtOAc/hexanes); IR (film) 3387, 3023, 2917, 2857 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.91 (br s, 1H), 7.22 (ddd, $J = 7.6, 7.6, 1.6$ Hz, 1H), 7.19 (dd, $J = 8.4, 1.6$ Hz, 1H), 6.93 (ddd, $J = 7.6, 1.2$ Hz, 1H), 6.86 (dd, $J = 8.0, 0.8$ Hz, 1H), 6.55 (s, 1H), 6.48 (s, 1H), 6.42 (s, 2H), 6.37 (s, 2H), 4.59 (br s, 1H), 4.48 (dd, $J = 9.6, 4.4$ Hz, 1H), 3.76 (br s, 1H), 3.60 (dd, $J = 13.2, 10.0$ Hz, 1H), 3.46 (dd, $J = 13.2, 4.4$ Hz, 1H), 2.27 (s, 6H), 2.19 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 156.9, 147.5, 146.7, 139.1, 138.9, 128.9, 128.0, 124.4, 123.1, 120.9, 120.1, 117.3, 114.6, 111.7, 60.4, 49.2, 21.5, 21.4; HRMS (ESI): Exact mass calcd for C$_{28}$H$_{37}$N$_2$O [M+H]$^+$ 417.2906, found 417.2917.

2-(1,2-Bis((4-fluorophenyl)amino)ethyl)phenol (338p). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). The aniline (85.0 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 1-
2-5-10-20-50% ethyl acetate in hexanes) afforded the desired product as a dark brown viscous oil (48.1 mg, 47%). R_f = 0.28 (20% EtOAc/hexanes); IR (film) 3310, 3040, 2926, 2858 1588, 1510 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.72 (br s, 1H), 7.23 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.16 (dd, J = 7.2, 1.2 Hz, 1H), 6.95-6.91 (m, 3H), 6.87-6.84 (m, 3H), 6.74-6.72 (m, 2H), 6.69-6.66 (m, 2H), 4.65 (br s, 1H), 4.44 (dd, J = 9.6, 4.2 Hz, 1H), 3.80 (br s, 1H), 3.56 (dd J = 13.2, 10.2 Hz, 1H), 3.46 (dd, J = 13.2, 4.8 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) ppm 158.0 (d, J = 239.6 Hz), 156.70, 156.65 (d, J = 236.9 Hz), 143.5, 142.7, 129.3, 128.1, 123.7, 120.3, 118.1 (d, J = 7.5 Hz), 117.4, 116.0 (d, J = 22.5 Hz), 115.8 (d, J = 22.6 Hz), 114.8 (J = 7.5 Hz), 60.7, 49.8; HRMS (ESI): Exact mass calcd for C₂₀H₁₉F₂N₂O [M+H]^+ 341.1460, found 314.1451.

1-(2-Hydroxyphenyl)-2-(isopropylamino)ethyl acetate (352). A 2-5 mL microwave vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 μmol), iodo benzene diacetate (193 mg, 600 μmol), and acetonitrile (3 mL). Isopropylamine (77.0 μL, 900 μmol) and 2-vinylphenol (36.0 mg, 300 μmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a brown viscous oil (18.2 mg, 26%). R_f = 0.33 (50% EtOAc/hexanes); IR (film) 3225, 2972, 2933, 1598 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 9.23 (br s, 1H), 7.17 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 7.02 (dd, J = 7.8, 1.8 Hz, 1H), 6.88 (dd, J = 7.8, 0.6 Hz, 1H), 6.83 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 6.54 (br s, 1H), 5.00 (d, J = 8.4 Hz, 1H), 4.07 (qq, J = 6.6, 6.6 Hz, 1H), 3.88 (dd, J = 15.6, 9.0 Hz, 1H), 3.24 (dd, J = 15.0, 1.2 Hz, 1H), 2.22 (s, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 174.0, 156.2, 129.0, 126.6, 125.3, 119.6, 117.5, 77.6, 50.4, 50.2, 21.8, 21.3, 20.6; HRMS (ESI): Exact mass calcd for C₁₃H₁₉NNaO₃ [M+Na]^+ 260.1263, found 260.1258. HSQC (600 MHz) and HMBC (600 MHz) analyses further confirmed the compound structure.
2-(Cyclohexylamino)-1-(2-hydroxyphenyl)ethyl acetate (353). A 2-5 mL microwave vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodosobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). Cyclohexylamine (103 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 20 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 25-50-75-100% ethyl acetate in hexanes) afforded the desired product as a gray-brown solid (23.8 mg, 29%). Mp 154.0-158.0 °C; Rₓ = 0.45 (50% EtOAc/hexanes); IR (film) 3126, 2924, 2853, 1570 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.17 (ddd, J = 9.0, 9.0, 1.8 Hz, 1H), 7.02 (dd, J = 7.8, 1.8 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.84 (ddd, J = 7.2, 7.2, 0.6 Hz, 1H), 4.97 (d, J = 7.8 Hz, 1H), 3.91 (dd, J = 15.0, 8.4 Hz, 1H), 3.55 (tt, J = 12.0, 3.6 Hz, 1H), 3.27 (dd, J = 15.0, 0.6 Hz, 1H), 2.21 (s, 3H), 1.94-1.88 (m, 2H), 1.86-1.81 (m, 1H), 1.71-1.64 (m, 2H), 1.52-1.44 (m, 1H), 1.43-1.28 (m, 3H), 1.13-1.05 (m, 1H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 174.2, 156.2, 128.9, 126.6, 125.3, 119.6, 117.5, 77.6, 59.2, 51.1, 31.8, 31.0, 25.9, 25.6, 25.0, 21.9; HRMS (ESI): Exact mass calcd for C₁₆H₂₃NNaO₃ [M+Na]+ 300.1576, found 300.1582. HSQC (600 MHz) and HMBC (600 MHz) analyses further confirmed the compound structure.

1-(2-Hydroxyphenyl)-2-((3-methoxypropyl)amino)ethyl acetate (354). A 2-5 mL microwave vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodosobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). 3-Methoxypropylamine (92.0 µL, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 25-50-75-100% ethyl acetate in hexanes) afforded the desired product as a light-brown viscous oil (26.5 mg, 33%). Rₓ = 0.17 (50% EtOAc/hexanes); IR (film) 3238, 2928, 1616 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.15 (ddd, J = 9.0, 9.0, 1.8 Hz, 1H), 7.07 (dd, J = 7.2, 1.2 Hz, 1H), 6.86 (dd, J = 8.4, 0.6 Hz, 1H), 6.83 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 5.15 (dd, J = 7.8, 2.4 Hz, 1H), 3.67 (dd, J = 14.4, 7.8 Hz, 1H), 3.53 (dd, J = 14.4, 2.4 Hz, 1H), 229
3.38-3.34 (m, 4H), 3.30 (s, 3H), 2.16 (s, 3H), 1.85-1.75 (m, 2H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 174.0, 155.7, 128.9, 126.4, 125.4, 119.6, 117.2, 74.0, 69.0, 58.6, 55.3, 48.3, 28.6, 21.2; HRMS (ESI): Exact mass calcd for C$_{14}$H$_{21}$NNaO$_4$ [M+Na]$^+$ 290.1368, found 290.1364. HSQC (600 MHz) and HMBC (600 MHz) analyses further confirmed the compound structure.

4-(1,2-Dimorpholinoethyl)phenol (340b). Prepared according to the general procedure using morpholine (78.0 µL, 900 µmol) and 4-vinylphenol (36.0 mg, 300 µmol). Flash column chromatography of the residue (SiO$_2$, 0.5-1-2-5-10% methanol in dichloromethane) afforded the desired product as a light-yellow viscous oil (51.9 mg, 59%). $R_f = 0.19$ (5% MeOH/DCM); IR (film) 3242 (br), 2959, 2857, 2820, 1613, 1595, 1516 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.07 (d, $J = 8.4$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 6.16 (br s, 1H), 3.73 (br dd, $J = 4.0$, 4.0 Hz, 4H), 3.69 (br dd, $J = 4.8$, 4.8 Hz, 5H), 3.12 (dd, $J = 12.8$, 6.8 Hz, 1H), 2.72 (dd, $J = 13.2$, 6.0 Hz, 1H), 2.62 (m, 4H), 2.52 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 155.5, 129.8, 115.2, 66.72, 66.67, 66.5, 61.3, 54.0, 51.0; Exact mass calcd for C$_{16}$H$_{25}$N$_2$O$_3$ [M+H]$^+$ 293.1865, found 293.1879.

![4-(1,2-Dimorpholinoethyl)phenol (340b)](image)

4-(1,2-Bis(phenylamino)ethyl)phenol (340c). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). Aniline (82.0 µL, 900 µmol) and 4-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 1-2-5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a brown viscous oil (78.0 mg, 85%). $R_f = 0.24$ (20% EtOAc/hexanes); IR (film) 3391, 3051, 3022, 1601, 1503 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25 (d, $J = 8.4$ Hz, 2H), 7.21 (dd, $J = 8.4$, 7.6 Hz, 2H), 7.12 (dd, $J = 8.4$, 7.6 Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 2H), 6.78 (dd, $J = 7.2$ Hz, 1H), 6.70 (dd, $J = 7.2$, 7.2 Hz, 1H), 6.66 (d, $J = 7.6$ Hz, 2H), 6.57 (d, $J = 8.0$ Hz, 2H), 4.59 (dd, $J = 7.6$, 5.2 Hz, 1H), 4.46 (br s, 2H), 3.47 (dd, $J = 12.4$, 4.8 Hz, 1H), 3.38 (dd, $J = 12.4$, 7.6 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) ppm 155.0, 147.8, 147.1, 133.2,
2-(1,2-Dithiomorpholinoethyl)-4-fluorophenol (338q). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 4-fluoro-2-vinylphenol (41.4 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a light-yellow solid (85.3 mg, 83%). Mp 72.0-76.0 °C; Rf = 0.38 (20% EtOAc/hexanes); IR (film) 3030(br), 2910, 2813, 1743, 1593 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.00 (br s, 1H), 6.87-6.79 (m, 2H), 6.73 (dd, J = 8.4, 4.8 Hz, 1H), 3.75 (dd, J = 6.0, 6.0 Hz, 1H), 3.09 (dd, J = 6.8, 3.2 Hz, 1H), 3.06 (dd, J = 6.0, 3.6 Hz, 1H), 2.92-2.86 (m, 3H), 2.77-2.72 (m, 4H), 2.72-2.67 (m, 4H), 2.66-2.62 (m, 5H); ¹³C NMR (150 MHz, CDCl₃) ppm 156.1 (d, Jₛₕ = 236.9 Hz), 153.2, 125.8 (d, Jₚₛₕ = 7.5 Hz), 117.4, 117.3, 114.9 (d, Jₚₛₕ = 16.9 Hz), 64.9, 58.4, 55.6, 51.9, 28.1, 27.9; HRMS (ESI): Exact mass calcd for C₁₆H₂₄FN₂O₃ [M+H]+ 343.1314, found 343.1329.

4-Chloro-2-(1,2-dithiomorpholinoethyl)phenol (338r). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (290 mg, 900 µmol), and acetonitrile (3 mL) and was chilled to 0 °C. Thiomorpholine (91.0 µL, 900 µmol) and 4-chloro-2-vinylphenol (46.4 mg, 300 µmol) were added and the resulting mixture was stirred at 0 °C for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-1-2-5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a light orange solid (69.1 mg, 64%). Mp 100.0-104.0 °C; Rf = 0.31 (20% EtOAc/hexanes); IR (film) 3030 (br), 2911, 2810, 1742, 1603, 1579 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 11.30 (br s, 1H), 7.10 (dd, J = 8.8, 2.4 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 3.72 (dd, J = 6.0, 6.0 Hz, 1H), 3.08 (dd, J = 7.2, 3.2 Hz, 1H), 3.05 (dd, J = 6.4, 3.6 Hz, 1H), 2.91-2.85 (m, 3H), 2.75-2.61 (m, 13H); ¹³C NMR (125 MHz, CDCl₃) ppm 156.0, 128.5,
128.3, 126.3, 123.7, 118.0, 58.6, 55.6, 52.0, 28.0, 27.9; HRMS (ESI): Exact mass calcd for C_{16}H_{24}ClN_{2}O_{2} [M+H]^+ 359.1019, found 359.1033.

4-Bromo-2-(1,2-dithiomorpholinoethyl)phenol (338s). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (290 mg, 900 µmol), and acetonitrile (3 mL) and was chilled to 0 °C. Thiomorpholine (91.0 µL, 900 µmol) and 4-bromo-2-vinylphenol (59.7 mg, 300 µmol) were added and the resulting mixture was stirred at 0 °C for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO_{2}, 0.5-1-2-5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a light yellow solid (85.1 mg, 70%). Mp 105.0-109.0 °C; R_{f} = 0.31 (20% EtOAc/hexanes); IR (film) 3030 (br), 2911, 2810, 1742, 1600, 1576 cm^{-1}; ^{1}H NMR (400 MHz, CDCl_{3}) δ 11.29 (br s, 1H), 7.24 (dd, J = 8.4, 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 3.72 (dd, J = 6.4, 6.4 Hz, 1H), 3.09 (dd, J = 6.8, 3.2 Hz, 1H), 3.06 (dd, J = 6.4, 3.6 Hz, 1H), 2.91-2.85 (m, 3H), 2.75-2.61 (m, 13H); ^{13}C NMR (125 MHz, CDCl_{3}) ppm 156.5, 131.5, 131.3, 126.8, 118.6, 110.9, 65.2, 58.6, 55.6, 52.0, 27.99, 27.97; HRMS (ESI): Exact mass calcd for C_{16}H_{24}BrN_{2}O_{2} [M+H]^+ 403.0513, found 403.0518.

2-(1,2-Dithiomorpholinoethyl)-4-nitrophenol (338t). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 4-nitro-2-vinylphenol (49.5 mg, 300 µmol). Flash column chromatography of the residue (SiO_{2}, 2-5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a viscous yellow oil (55.1 mg, 50%). R_{f} = 0.10 (20% EtOAc/hexanes); IR (film) 3060 (br), 2910, 2813, 1615, 1586 cm^{-1}; ^{1}H NMR (400 MHz, CDCl_{3}) δ 8.12 (d, J = 2.8 Hz, 1H), 8.07 (dd, J = 8.8, 2.0 Hz, 1H), 6.83 (d, J = 9.2 Hz, 1H), 3.88 (dd, J = 7.6, 4.8 Hz, 1H), 3.13-3.08 (m, 2H), 2.95-2.89 (m, 3H), 2.87-2.65 (m, 13H); ^{13}C NMR (125 MHz, CDCl_{3}) ppm 164.3, 140.0, 125.2 (2C), 124.7, 117.1, 64.6, 57.7, 55.6, 51.6, 28.0, 27.9; HRMS (ESI): Exact mass calcd for C_{16}H_{24}N_{3}O_{3}S_{2} [M+H]^+ 370.1259, found 370.1265.
2-(1,2-Dithiomorpholinoethyl)-4-methoxyphenol (338u). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 4-methoxy-2-vinylphenol (45.1 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 20-40% ethyl acetate in hexanes) afforded the desired product as an off-white solid (57.0 mg, 54%). Mp 114.0-116.0 °C; R_f = 0.25 (20% EtOAc/hexanes); IR (film) 2908, 2828, 1492 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 10.56 (br s, 1H), 6.74-6.70 (m, 2H), 6.64 (d, J = 2.4 Hz, 1H), 3.74 (s, 3H), 3.72 (dd, J = 6.0 Hz, 1H), 3.08 (dd, J = 7.8, 3.0 Hz, 1H), 3.06 (dd, J = 6.6, 3.0 Hz, 1H), 2.91-2.86 (m, 3H), 2.77-2.60 (m, 13H); ¹³C NMR (150 MHz, CDCl₃) ppm 152.5, 150.9, 125.7, 117.0, 114.6, 113.2, 65.4, 59.0, 55.7, 55.6, 52.1, 28.03, 27.97; HRMS (ESI): Exact mass calcd for C₁₇H₂₇N₂O₂S₂ [M+H]^+ 355.1514, found 355.1521.

2-(1,2-Dithiomorpholinoethyl)benzene-1,4-diol (338v). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 2-vinylbenzene-1,4-diol (40.9 mg, 300 µmol). Flash column chromatography of the residue (SiO₂, 50-75-100% ethyl acetate in hexanes) afforded the desired product as a light-brown viscous oil (23.8 mg, 23%). R_f = 0.35 (5% MeOH/DCM); IR (film) 3300 (br), 2911, 2817, 2362, 1731, 1560 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.68 (d, J = 8.4 Hz, 1H), 6.64 (dd, J = 8.8, 2.8 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 3.71 (dd, J = 6.0, 6.0 Hz, 1H), 3.07 (ddd, J = 10.4, 6.4, 3.6 Hz, 2H), 2.89 (m, 3H), 2.70 (m, 13H); ¹³C NMR (150 MHz, CDCl₃) ppm 150.8, 148.3, 125.8, 117.3, 115.4, 115.3, 65.2, 59.0, 55.6, 52.1, 28.0, 27.9; Exact mass calcd for C₁₆H₂₅N₂O₂S₂ [M+H]^+ 341.1357, found 341.1365.

2-(1,2-Dithiomorpholinoethyl)-5-methoxyphenol (338w). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 5-methoxy-2-vinylphenol (45.1 mg, 300
μmol). The residue was diluted with dichloromethane and filtered through a silica plug with dichloromethane and ethyl acetate and then concentrated. Flash column chromatography of the residue (SiO\(_2\), 1-2.5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a yellow-orange viscous oil (60.2 mg, 57%). \( R_f = 0.25 \) (40% EtOAc/hexanes); IR (film) 3020 (br), 2911, 2833, 1619, 1587, 1508 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 11.31 (br s, 1H), 6.92 (d, \( J = 8.4 \) Hz, 1H), 6.38 (d, \( J = 2.4 \) Hz, 1H), 6.36 (dd, \( J = 8.4, 2.8 \) Hz, 1H), 3.79-3.73 (m, 1H), 3.76 (s, 3H), 3.10 (dd, \( J = 6.8, 3.2 \) Hz, 1H), 3.07 (dd, \( J = 6.4, 4.0 \) Hz, 1H), 2.92-2.83 (m, 3H), 2.76-2.62 (m, 13 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) ppm 160.3, 158.5, 128.9, 116.9, 105.0, 102.1, 64.9, 58.9, 55.6, 55.1, 51.8, 28.0, 27.9; HRMS (ESI): Exact mass calcd for C\(_{17}\)H\(_{27}\)N\(_2\)O\(_2\)S\(_2\) [M+H]\(^+\) 355.1514, found 355.1528.

2-(1,2-Dithiomorpholinoethyl)-6-methoxyphenol (338x). Prepared according to the general procedure using thiomorpholine (91.0 µL, 900 µmol) and 2-methoxy-6-vinylphenol (45.1 mg, 300 µmol). Flash column chromatography of the residue (SiO\(_2\), 5-10-20-40-80% ethyl acetate in hexanes) afforded the desired product as an off-white solid (88.7 mg, 83%). Mp 115.0-118.0 °C; \( R_f = 0.10 \) (20% EtOAc/hexanes); IR (film) 3020 (br), 2908, 2829, 1585 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.65 (br s, 1H), 6.79 (dd, \( J = 8.4, 1.6 \) Hz, 1H), 6.73 (dd, \( J = 7.6, 7.6 \) Hz, 1H), 6.64 (dd, \( J = 8.0, 1.6 \) Hz, 1H), 3.85 (s, 3H), 3.82 (dd, \( J = 6.4, 6.4 \) Hz, 1H), 3.09 (dd, \( J = 6.8, 2.8 \) Hz, 1H), 3.05 (dd, \( J = 6.4, 3.2 \) Hz, 1H), 2.94-2.86 (m, 3H), 2.80-2.71 (m, 4H), 2.71-2.65 (m, 5H), 2.65-2.59 (m, 4H); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) ppm 148.2, 146.6, 125.0, 120.2, 118.6, 110.7, 65.3, 59.3, 55.8, 55.5, 52.1, 28.0, 27.9; HRMS (ESI): Exact mass calcd for C\(_{17}\)H\(_{27}\)N\(_2\)O\(_2\)S\(_2\) [M+H]\(^+\) 355.1514, found 355.1521.

2,3-Dihydrobenzofuran-3-yl acetate (355). A 2-5 mL microwave vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). 2-Vinylphenol (36.0 mg, 300 µmol) was added and the resulting
mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 2-20% diethyl ether in hexanes) afforded the desired product as a light yellow transparent viscous oil (36.8 mg, 69%). $R_f = 0.37$ (20% Et$_2$O/hexanes); IR (film) 3054, 2948, 2884, 1737, 1612, 1600 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 (dd, $J = 7.6, 0.4$ Hz, 1H), 7.30 (dd, $J = 8.4, 8.4, 1.2$ Hz, 1H), 6.95 (dd, $J = 7.2, 7.2$ Hz, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.25 (dd, $J = 6.8, 2.4$ Hz, 1H), 4.62 (dd, $J = 11.6, 6.8$ Hz, 1H), 4.51 (dd, $J = 11.2, 2.4$ Hz, 1H), 2.07 (s, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) ppm 170.8, 161.0, 131.3, 126.7, 124.3, 121.0, 110.5, 76.0, 74.2, 21.0; HRMS (CI): Exact mass calcd for C$_{10}$H$_{10}$O$_3$ [M]$^+$ 178.0624, found 178.0623.

1-(2-hydroxyphenyl)-2-iodoethyl acetate (356). A vial equipped with a stir bar was charged with potassium iodide (60.0 mg, 360 µmol), iodobenzene diacetate (193 mg, 600 µmol), and acetonitrile (3 mL). Bistosylimide (293 mg, 900 µmol) and 2-vinylphenol (36.0 mg, 300 µmol) were added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 2-5-10-20-50-100% diethyl ether in hexanes) afforded the desired product as a yellow-orange viscous oil (11.3 mg, 12%). $R_f = 0.76$ (80% Et$_2$O/hexanes); IR (film) 3396 (br), 2923, 2852, 1719, 1598 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 7.24 (ddd, $J = 9.6, 9.6, 1.8$ Hz, 2H), 6.95 (ddd, $J = 7.2, 7.2, 0.6$ Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 6.42 (br s, 1H), 6.07 (dd, $J = 9.0, 4.8$ Hz, 1H), 3.65 (dd, $J = 10.2, 9.0$ Hz, 1H), 3.55 (dd, $J = 10.8, 4.8$ Hz, 1H), 2.16 (s, 3H); $^{13}$C NMR (150.9 MHz, CDCl$_3$) ppm 171.2, 153.7, 130.4, 126.8, 124.3, 121.1, 117.5, 71.9, 20.9, 5.6; HRMS (ESI): no mass was observed due to decomposition upon multiple submissions.

**General procedure for Hypervalent Iodine-Mediated Intra/Intermolecular Diamination:** To a vial equipped with a stir bar was added PhI(OAc)$_2$ (72.5 mg, 225 µmol), KI (24.9 mg, 150 µmol), the vinyl aminopyridine (41.2 mg, 150 µmol), and acetonitrile (1.5 mL). The amine (300 µmol) was added and the resulting mixture was allowed to stir at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. No reductive workup was used in these studies,
but is recommended for a larger scale. EtOAc was used to transfer the heterogeneous reaction mixture to a larger flask for concentration. After concentration, the resulting residue was then subjected to flash column chromatography.

**N-Phenyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-amine (521a).** A vial equipped with a stir bar was charged with potassium iodide (33.2 mg, 200 µmol), iodobenzene diacetate (96.6 mg, 300 µmol), 4-methyl-N-(3-vinylpyridin-2-yl)benzenesulfonamide (55.0 mg, 200 µmol), and acetonitrile (2 mL). Aniline (36.5 µL, 400 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a light-brown solid (70.4 mg, 96%). Mp 194.0-196.0 °C; Rᵣ = 0.54 (50% EtOAc/hexanes); IR (film) 3386, 3052, 2924, 2340, 1923, 1601 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.31 (dd, J = 5.4, 1.2 Hz, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.56 (ddd, J = 7.2, 1.2, 1.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.21 (dd, J = 8.4, 7.2 Hz, 2H), 6.90 (dd, J = 7.8, 5.4 Hz, 1H), 6.81 (dd, J = 7.2, 7.2 Hz, 1H), 6.59 (d, J = 7.2 Hz, 2H), 5.05 (br s, 1H), 4.27 (dd, J = 10.8, 7.8 Hz, 1H), 3.92 (dd, J = 10.8, 4.8 Hz, 1H), 3.76 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃) ppm 155.8, 149.3, 145.5, 144.3, 134.9, 133.9, 129.6, 129.5, 128.1, 124.7, 119.0, 118.4, 113.6, 55.4, 50.9, 21.6; HRMS (ESI): Exact mass calcd for C₂₀H₂₀N₃O₂S [M+H]⁺ 366.1276, found 366.1272.

**N-Benzyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-amine (521b).** Prepared according to the general procedure using benzylamine (32.8 µL, 300 µmol) and 4-methyl-N-(3-vinylpyridin-2-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO₂, 10-30-60% ethyl acetate in hexanes) afforded the desired product as an orange viscous oil (41.8 mg, 73%). Rᵣ = 0.28 (50% EtOAc/hexanes); IR (film) 3319, 3060, 3029, 2923, 1597 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, J = 5.2, 1.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.27-7.16 (m, 7H), 6.81 (dd, J = 7.2, 4.8 Hz, 1H), 4.23 (dd, J = 8.0, 4.4 Hz, 1H), 4.01 (dd, J = 10.4, 8.0 Hz, 1H), 3.86 (dd, J = 10.8, 4.4 Hz, 1H), 3.72 (s, 2H), 2.28 (s, 3H), 1.57 (br
$^{13}$C NMR (100 MHz, CDCl$_3$) ppm 155.7, 148.6, 144.2, 139.2, 134.9, 133.8, 129.4, 128.5, 128.0, 127.96, 127.3, 125.8, 118.2, 55.1, 54.6, 50.5, 21.5; HRMS (ESI): Exact mass calcd for C$_{21}$H$_{22}$N$_3$O$_2$S [M+H]$^+$ 380.1433, found 380.1430.

$N$-Allyl-1-tosyl-2,3-dihydro-$1H$-pyrrolo[2,3-b]pyridin-3-amine (521c). Prepared according to the general procedure using allylamine (22.4 µL, 300 µmol) and 4-methyl-$N$-(3-vinylpyridin-2-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO$_2$, 50-70-90% ethyl acetate in hexanes) afforded the desired product as an orange-brown viscous oil (30.8 mg, 62%). $R_f$ = 0.12 (50% EtOAc/hexanes); IR (film) 3317, 3065, 2924, 1596 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.24 (dd, $J$ = 4.8, 1.2 Hz, 1H), 7.96 (d, $J$ = 8.4 Hz, 2H), 7.54 (d, $J$ = 6.8 Hz, 1H), 7.25 (d, $J$ = 7.6 Hz, 2H), 6.87 (dd, $J$ = 7.6, 5.2 Hz, 1H), 5.86 (dddd, $J$ = 11.6, 10.4, 6.0, 6.0 Hz, 1H), 5.20 (dd, $J$ = 17.2, 1.6 Hz, 1H), 5.12 (dd, $J$ = 10.4, 1.2 Hz, 1H), 4.29 (dd, $J$ = 8.0, 4.0 Hz, 1H), 4.06 (dd, $J$ = 10.8, 8.0 Hz, 1H), 3.88 (dd, $J$ = 10.8, 4.4 Hz, 1H), 3.27 (d, $J$ = 6.0, 0.8 Hz, 2H), 2.37 (s, 3H), 1.62 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 155.6, 148.7, 144.2, 135.8, 134.9, 133.8, 129.4, 128.0, 125.7, 118.2, 116.8, 55.1, 54.6, 49.1, 21.5; HRMS (ESI): Exact mass calcd for C$_{17}$H$_{19}$N$_3$NaO$_2$S [M+Na]$^+$ 352.1096, found 352.1082.

4-(1-Tosyl-2,3-dihydro-$1H$-pyrrolo[2,3-b]pyridin-3-yl)thiomorpholine (521d). A vial equipped with a stir bar was charged with potassium iodide (29.9 mg, 180 µmol), iodosobenzene diacetate (96.6 mg, 300 µmol), 4-methyl-$N$-(3-vinylpyridin-2-yl)benzenesulfonamide (41.2 mg, 150 µmol), and acetonitrile (1.5 mL). Thiomorpholine (45.3 µL, 450 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 20-50-80% ethyl acetate in hexanes) afforded the desired product as a light-brown solid (21.8 mg, 39%). Mp 182.0-186.0 °C; $R_f$ = 0.27 (50% EtOAc/hexanes); IR (film) 3054, 2921, 2821, 1644, 1594 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.27 (dd, $J$ = 4.8, 1.2 Hz, 1H), 7.97 (d, $J$ = 8.4 Hz, 2H), 7.51 (d, $J$ = 7.2 Hz, 1H), 7.26 (d, $J$ = 8.0 Hz, 2H), 6.89 (dd, $J$ = 7.6, 5.2 Hz, 1H), 4.28 (dd, $J$ = 9.6, 4.0 Hz, 1H), 4.12 (dd, $J$ = 9.6, 4.0 Hz, 1H), 4.06 (dd, $J$ = 10.8, 4.4 Hz, 1H), 3.88 (dd, $J$ = 10.8, 4.4 Hz, 1H), 3.27 (d, $J$ = 6.0, 0.8 Hz, 2H), 2.37 (s, 3H), 1.62 (br s, 1H).
= 11.2, 4.0 Hz, 1H), 3.86 (dd, J = 11.2, 9.2 Hz, 1H), 2.78-2.70 (m, 2H), 2.63-2.53 (m, 6H), 2.38 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 156.3, 149.0, 144.3, 135.1, 134.8, 129.5, 128.0, 122.6, 118.1, 62.8, 50.7, 49.0, 28.2, 21.6; HRMS (ESI): Exact mass calcd for C$_{18}$H$_{22}$N$_3$O$_2$S$_2$ [M+H]$^+$ 376.1153, found 376.1154.

4-(1-Tosyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-3-yl)morpholine (521e). Prepared according to the general procedure using morpholine (26.0 µL, 300 µmol) and 4-methyl-N-(3-vinylpyridin-2-yl)benzenesulfonylamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO$_2$, 50-70-90% ethyl acetate in hexanes) afforded the desired product as a dark-yellow solid (30.8 mg, 57%). Mp 161.0-165.0 °C; R$_f$ = 0.10 (50% EtOAc/hexanes); IR (film) 2923, 2854, 1593 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.28 (dd, J = 5.2, 1.6 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.91 (dd, J = 7.2, 5.2 Hz, 1H), 4.27 (dd, J = 9.2, 3.6 Hz, 1H), 4.15 (dd, J = 11.6, 3.6 Hz, 1H), 3.83 (dd, J = 11.2, 9.2 Hz, 1H), 3.61 (dd, J = 4.8, 4.8 Hz, 4H), 2.49-2.44 (m, 2H), 2.37 (s, 3H), 2.31-2.26 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 156.3, 149.1, 144.4, 135.2, 134.8, 129.5, 127.9, 122.4, 118.2, 66.8, 61.4, 48.8, 48.4, 21.6; HRMS (ESI): Exact mass calcd for C$_{18}$H$_{22}$N$_3$O$_3$S [M+H]$^+$ 360.1382, found 360.1378.

$N$-Phenyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-3-amine (524a). A vial equipped with a stir bar was charged with potassium iodide (6.70 mg, 40.5 µmol), iodosobenzene diacetate (19.6 mg, 60.7 µmol), the vinyl aminopyridine (11.1 mg, 40.5 µmol), and acetonitrile (405 µL). Aniline (7.40 µL, 80.9 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 5-10-20-40-80% ethyl acetate in hexanes) afforded the desired product as a dark brown viscous oil (1.6 mg, 11%). R$_f$ = 0.62 (70% EtOAc/hexanes); IR (film) 3380, 3050, 2922, 2851, 1600 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.02 (s, 1H), 8.35 (d, J = 4.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 6.0 Hz, 2H), 7.20 (m, 3H), 6.81 (dd, J = 7.2, 7.2 Hz, 1H), 6.47 (d, J =
7.6 Hz, 2H), 4.97 (br m, 1H), 4.16 (dd, J = 11.6, 8.0 Hz, 1H), 3.78 (d, J = 11.6, 4.8 Hz, 1H), 3.34 (br d, J = 8.0 Hz, 1H), 2.41 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) ppm 145.3, 145.2, 144.8, 140.8, 139.0, 137.4, 133.2, 130.0, 129.6, 127.4, 120.0, 119.2, 113.5, 56.2, 53.3, 21.6; HRMS (ESI): Exact mass calcd for C\(_{20}\)H\(_{20}\)N\(_3\)O\(_2\)S [M+H]\(^+\) 366.1276, found 366.1284.

**N-Benzyl-1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-3-amine (524b).** A vial equipped with a stir bar was charged with potassium iodide (7.80 mg, 47.0 µmol), iodobenzene diacetate (22.9 mg, 71.0 µmol), 4-methyl-N-(4-vinylpyridin-3-yl)benzenesulfonamide (12.9 mg, 47.0 µmol), and acetonitrile (470 µL). Benzylamine (10.3 µL, 94.0 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO\(_2\), 40-60-80% ethyl acetate in hexanes) afforded the desired product as a yellow-orange viscous oil (8.60 mg, 48%). R\(_f\) = 0.22 (70% EtOAc/hexanes); IR (film) 3032, 2924, 2854, 2360, 2341, 1596 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.98 (s, 1H), 8.34 (br d, J = 4.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.34-7.18 (m, 8H), 4.23 (dd, J = 8.0, 4.4 Hz, 1H), 3.95 (dd, J = 11.6, 8.0 Hz, 1H), 3.77 (dd, J = 11.2, 4.4 Hz, 1H), 3.66 (s, 2H), 2.30 (s, 3H), 1.53 (br s, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) ppm 145.1, 144.8, 141.9, 139.0, 138.9, 137.1, 133.2, 129.9, 128.5, 128.0, 127.4, 127.3, 120.1, 57.1, 55.7, 50.7, 21.5; HRMS (ESI): Exact mass calcd for C\(_{21}\)H\(_{22}\)N\(_3\)O\(_2\)S [M+H]\(^+\) 380.1433, found 380.1427.

**Benzyl 4-(1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-3-yl)piperazine-1-carboxylate (524c).** A vial equipped with a stir bar was charged with potassium iodide (8.3 mg, 50.0 µmol), iodobenzene diacetate (24.2 mg, 75.0 µmol), 4-methyl-N-(4-vinylpyridin-3-yl)benzenesulfonamide (13.7 mg, 50.0 µmol), and acetonitrile (500 µL). Benzyl piperazine-1-carboxylate (19.3 µL, 100 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO\(_2\), 50-70-90% ethyl acetate in hexanes) afforded the desired product as a yellow-orange viscous oil (12.9 mg, 20%). R\(_f\) = 0.22 (70% EtOAc/hexanes); IR (film) 3032, 2924, 2854, 2360, 2341, 1596 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.98 (s, 1H), 8.34 (br d, J = 4.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.34-7.18 (m, 8H), 4.23 (dd, J = 8.0, 4.4 Hz, 1H), 3.95 (dd, J = 11.6, 8.0 Hz, 1H), 3.77 (dd, J = 11.2, 4.4 Hz, 1H), 3.66 (s, 2H), 2.30 (s, 3H), 1.53 (br s, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) ppm 145.1, 144.8, 141.9, 139.0, 138.9, 137.1, 133.2, 129.9, 128.5, 128.0, 127.4, 127.3, 120.1, 57.1, 55.7, 50.7, 21.5; HRMS (ESI): Exact mass calcd for C\(_{21}\)H\(_{22}\)N\(_3\)O\(_2\)S [M+H]\(^+\) 380.1433, found 380.1427.
product as a clear viscous oil (15.6 mg, 63%). Rf = 0.48 (5% MeOH/DCM); IR (film) 3033, 2925, 2860, 2822, 2360, 2336, 1699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.00 (br s, 1H), 8.31 (br d, J = 4.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.39-7.29 (m, 5H), 7.25 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 4.8 Hz, 1H), 5.10 (s, 2H), 4.34 (dd, J = 9.2, 4.0 Hz, 1H), 3.88 (dd, J = 11.6, 4.4 Hz, 1H), 3.71 (dd, J = 11.6, 9.2 Hz, 1H), 3.36 (br d, J = 4.8 Hz, 4H), 2.35 (s, 3H), 2.29-2.22 (m, 2H), 2.21-2.02 (br m, 2H); ¹³C NMR (125 MHz, CDCl₃) ppm 155.0, 144.9, 144.6, 139.6, 138.1, 136.5, 136.3, 133.2, 130.0, 128.5, 128.1, 127.9, 127.3, 120.9, 67.2, 63.8, 49.5, 47.8, 43.7, 21.5; HRMS (ESI): Exact mass calcd for C₂₆H₂₉N₄O₄S [M+H]⁺ 493.1910, found 493.1901.

Ethyl 4-(1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-3-yl)piperazine-1-carboxylate (524d).

A vial equipped with a stir bar was charged with potassium iodide (13.9 mg, 83.8 µmol), iodobenzene diacetate (40.6 mg, 126 µmol), 4-methyl-N-(4-vinylpyridin-3-yl)benzenesulfonamide (23.0 mg, 83.8 µmol), and acetonitrile (840 µL). Ethyl 1-piperazinecarboxylate (24.5 µL, 168 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a dark-yellow viscous oil (23.8 mg, 66%). Rf = 0.52 (5% MeOH/DCM); IR (film) 3053, 2981, 2931, 2863, 2822, 2763, 1697, 1596 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H), 8.31 (d, J = 4.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 4.8 Hz, 1H), 4.34 (dd, J = 9.6, 6.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.89 (dd, J = 11.6, 4.4 Hz, 1H), 3.71 (d, J = 11.6, 9.2 Hz, 1H), 3.33 (dd, J = 4.8, 4.8 Hz, 4H), 2.39 (s, 3H), 2.26 (ddd, J = 10.4, 4.8, 4.8 Hz, 2H), 2.19-2.05 (br s, 2H), 1.24 (t, J = 6.8 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 155.3, 144.9, 144.6, 139.6, 138.1, 136.3, 133.2, 130.0, 127.3, 120.9, 63.8, 61.4, 49.6, 48.0, 43.6, 21.5, 14.6; HRMS (ESI): Exact mass calcd for C₂₁H₂₇N₄O₄S [M+H]⁺ 431.1753, found 431.1750.
**tert-Butyl 4-(1-tosyl-2,3-dihydro-1H-pyrrolo[2,3-c]pyridin-3-yl)piperazine-1-carboxylate (524e).** A vial equipped with a stir bar was charged with potassium iodide (8.3 mg, 50.0 µmol), iodobenzene diacetate (24.2 mg, 75.0 µmol), 4-methyl-N-(4-vinylpyridin-3-yl)benzenesulfonamide (13.7 mg, 50.0 µmol), and acetonitrile (500 µL). tert-Butyl piperazine-1-carboxylate (18.6 mg, 100 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 50-70-90% ethyl acetate in hexanes) afforded the desired product as a light-yellow transparent viscous oil (17.0 mg, 74%). Rf = 0.22 (80% EtOAc/Hexanes); IR (film) 2975, 2929, 2861, 2822, 2360, 2337, 1692 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.99 (br s, 1H), 8.31 (br d, J = 4.8 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 4.8 Hz, 1H), 4.34 (dd, J = 9.2, 4.0 Hz, 1H), 3.90 (dd, J = 11.6, 4.4 Hz, 1H), 3.71 (d, J = 11.6, 9.2 Hz, 1H), 3.32-3.23 (br m, 4H), 2.39 (s, 3H), 2.28-2.21 (m, 2H), 2.19-2.00 (br m, 2H), 1.43 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) ppm 154.5, 144.9, 144.6, 139.6, 138.1, 136.3, 133.2, 130.0, 127.4, 120.9, 79.8, 63.8, 49.7, 48.1 (br), 43.8 (br), 28.4, 21.6; HRMS (ESI): Exact mass calcd for C₂₃H₃₁N₄O₄S [M+H]^+ 459.2066, found 459.2056.

**N-Phenyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527a).** A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodobenzene diacetate (36.2 mg, 113 µmol), 4-methyl-N-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). Aniline (13.7 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-1-2% methanol in dichloromethane) afforded the desired product as a light-brown solid (22.2 mg, 81%). Mp 194.0-196.0 °C; Rf = 0.52 (5% MeOH/DCM); IR (film) 3393, 3249, 3106, 3030, 2924, 1600 cm⁻¹; ¹H NMR (400 MHz, CDCl₃)
δ 8.50 (d, J = 5.6 Hz, 1H), 8.47 (s, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 5.6 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.20 (dd, J = 8.4, 7.6 Hz, 2H), 6.81 (dd, J = 7.2, 7.2 Hz, 1H), 6.51 (d, J = 7.6 Hz, 2H), 5.07 (br s, 1H), 4.13 (dd, J = 11.2, 7.6 Hz, 1H), 3.86 (dd, J = 11.2, 3.6 Hz, 1H), 3.57 (br s, 1H); 13C NMR (125 MHz, CDCl3) ppm 151.2, 149.3, 147.1, 145.3, 145.0, 133.6, 130.1, 129.6, 127.5, 127.2, 119.0, 113.4, 109.3, 56.8, 51.8, 21.6; HRMS (ESI): Exact mass calcd for C20H19N3O2S [M+] 365.1192, found 365.1192.

**N-Benzyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527b).** A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodobenzene diacetate (36.2 mg, 113 µmol), the vinyl aminopyridine (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). Benzylamine (16.4 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO2, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a yellow viscous oil (12.3 mg, 43%). Rf = 0.51 (5% MeOH/DCM); IR (film) 3027, 2922, 2852, 2359, 2337,1595, cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 8.46 (br s, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 5.6 Hz, 1H), 7.34-7.29 (m, 2H), 7.28-7.22 (m, 5H), 4.36 (dd, J = 8.0, 4.0 Hz, 1H), 3.93 (dd, J = 11.2, 8.0 Hz, 1H), 3.84 (dd, J = 11.2, 4.0 Hz, 1H), 3.70 (s, 2H), 2.60 (br s, 1H), 2.34 (s, 3H); 13C NMR (100 MHz, CDCl3) ppm 150.4, 149.2, 146.6, 145.0, 139.0, 133.5, 130.0, 128.5, 128.0, 127.4, 127.1, 109.2, 56.2, 55.6, 50.4, 21.5; HRMS (ESI): Exact mass calcd for C21H22N3O2S [M+H]+ 380.1433, found 380.1416.

**N-(4-Methylbenzyl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527c).** A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodobenzene diacetate (36.2 mg, 113 µmol), 4-methyl-N-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). 4-Methylbenzylamine (19.1 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO2, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a clear viscous oil (13.2 mg, 45%).
RF = 0.46 (5% MeOH/DCM); IR (film) 3321, 3028, 2923, 2855, 2732, 1595 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.45 (br s, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.13 (s, 4H), 4.34 (dd, J = 8.0, 3.6 Hz, 1H), 3.92 (dd, J = 10.8, 7.6 Hz, 1H), 3.83 (dd, J = 11.2, 4.0 Hz, 1H), 3.66 (s, 2H), 2.35 (s, 3H), 2.33 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 150.6, 149.0, 146.8, 144.9, 136.9, 135.9, 133.5, 129.9, 129.1, 128.6, 127.9, 127.1, 109.1, 56.1, 55.5, 50.1, 21.5, 21.0; HRMS (ESI): Exact mass calcd for C₂₂H₂₄N₃O₂S [M+H]+ 394.1589, found 394.1571.

N-(4-Fluorobenzyl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527d). A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodo benzene diacetate (36.2 mg, 113 µmol), 4-methyl-N-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). 4-Fluorobenzylamine (17.1 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a light-yellow transparent viscous oil (15.3 mg, 51%). RF = 0.48 (5% MeOH/DCM); IR (film) 3256, 3041, 2925, 2853, 2357, 2336, 1596 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.47 (br s, 1H), 8.45 (s, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 5.6 Hz, 1H), 7.27-7.19 (m, 4H), 6.99 (dd, J = 8.8, 8.8 Hz, 2H), 4.34 (dd, J = 8.0, 3.6 Hz, 1H), 3.92 (dd, J = 11.2, 8.0 Hz, 1H), 3.84 (dd, J = 11.2, 3.6 Hz, 1H), 3.67 (s, 2H), 2.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 162.1 (d, J = 245.3 Hz), 150.8, 149.1, 146.9, 145.0, 134.8 (d, J = 3.0 Hz), 133.6, 130.0, 129.5 (d, J = 7.9 Hz), 128.5, 127.2, 115.3 (d, J = 21.4 Hz), 109.2, 56.1, 55.6, 49.6, 21.5; HRMS (ESI): Exact mass calcd for C₂₁H₁₈FN₃O₂S [M-2H]- 395.1098, found 395.1085.

N-(3-Methoxypropyl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527e). A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodo benzene diacetate (36.2 mg, 113 µmol), 4-methyl-N-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). 3-Methoxypropylamine (15.3 µL, 150 µmol) was added
and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a light-brown viscous oil (13.0 mg, 48%). $R_f = 0.29$ (5% MeOH/DCM); IR (film) 3249, 3036, 2926, 2873, 1644, 1596 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.44 (s, 1H), 8.43 (s, 1H), 7.73 (d, $J = 7.8$ Hz, 2H), 7.54 (d, $J = 5.4$ Hz, 1H), 7.28 (d, $J = 8.4$ Hz, 2H), 4.34 (dd, $J = 7.8$, 3.6 Hz, 1H), 3.91 (dd, $J = 10.8$, 7.8 Hz, 1H), 3.80 (dd, $J = 10.8$, 3.6 Hz, 1H), 3.38 (dd, $J = 6.0$, 6.0 Hz, 2H), 3.29 (s, 3H), 2.66-2.58 (m, 2H), 2.39 (s, 3H), 1.66 (dddd, $J = 6.6$, 6.6, 6.6, 6.6 Hz, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$) ppm 150.6, 149.1, 146.8, 144.9, 133.6, 130.0, 128.4, 127.2, 109.0, 71.0, 58.7, 56.3, 56.1, 43.9, 29.9, 21.6; HRMS (ESI): Exact mass calcd for C$_{18}$H$_{24}$N$_3$O$_3$S [M+H]$^+$ 362.1538, found 362.1537.

$N$-Phenethyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527f). A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodo benzene diacetate (36.2 mg, 113 µmol), 4-methyl-$N$-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). Phenethylamine (18.8 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as an orange viscous oil (14.1 mg, 48%). $R_f = 0.42$ (5% MeOH/DCM); IR (film) 3312, 3028, 2925, 2855, 1637, 1596 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.42 (d, $J = 5.6$ Hz, 1H), 8.36 (s, 1H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 5.6$ Hz, 1H), 7.31-7.19 (m, 5H), 7.13 (dd, $J = 8.4$, 1.6 Hz, 2H), 4.36 (dd, $J = 8.0$, 4.0 Hz, 1H), 3.90 (dd, $J = 11.2$, 8.4 Hz, 1H), 3.76 (dd, $J = 11.2$, 4.0 Hz, 1H), 2.83-2.67 (m, 4H), 2.39 (br s, 1H), 2.39 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 150.5, 149.1, 146.7, 144.9, 139.3, 133.6, 130.0, 128.59, 128.57, 128.3, 127.2, 126.4, 109.0, 56.14, 56.09, 47.4, 36.4, 21.6; HRMS (ESI): Exact mass calcd for C$_{22}$H$_{24}$N$_3$O$_2$S [M+H]$^+$ 394.1587, found 394.1587.
**N-(Tetrahydro-2H-pyran-4-yl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527g).** A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodo benzene diacetate (36.2 mg, 113 µmol), 4-methyl-N-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). 4-Aminotetrahydropyran (15.5 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO\(_2\), 0.5-1-2-5-10% methanol in dichloromethane) afforded the desired product as a light-yellow viscous oil (9.20 mg, 33%). R\(_f\) = 0.35 (5% MeOH/DCM); IR (film) 3299, 3046, 2927, 2850, 1596 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.44 (br d, \(J\) = 5.2 Hz, 1H), 8.40 (br s, 1H), 7.73 (d, \(J\) = 8.4 Hz, 2H), 7.55 (d, \(J\) = 5.2 Hz, 1H), 7.29 (d, \(J\) = 8.0 Hz, 2H), 4.42 (dd, \(J\) = 8.0, 4.0 Hz, 1H), 3.95 (dd, \(J\) = 10.8, 7.6 Hz, 1H), 3.98-3.91 (br m, 2H), 3.74 (dd, \(J\) = 10.8, 4.0 Hz, 1H), 3.42-3.33 (m, 2H), 2.78 (ddddd, \(J\) = 10.0, 3.6, 3.6, 3.6, 3.6 Hz, 1H), 2.40 (s, 3H), 1.73-1.64 (br m, 2H), 1.49 (br s, 1H), 1.44-1.32 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) ppm 150.6, 148.9, 146.7, 145.0, 133.6, 130.0, 129.0, 127.2, 109.1, 66.33, 66.30, 57.2, 53.0, 51.3, 33.9, 33.4, 21.6; HRMS (ESI): Exact mass calcd for C\(_{19}\)H\(_{24}\)N\(_3\)O\(_3\)S [M+H]\(^+\) 374.1538, found 374.1534.

**N-(Pyridin-3-ylmethyl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-amine (527h).** A vial equipped with a stir bar was charged with potassium iodide (39.8 mg, 240 µmol), iodo benzene diacetate (96.6 mg, 300 µmol), 4-methyl-N-(3-vinylpyridin-4-yi)benzenesulfonamide (54.8 mg, 200 µmol), and acetonitrile (2 mL). 3-Picolylamine (40.4 µL, 400 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO\(_2\), 0.5-1-2-5-10% methanol in dichloromethane) afforded the desired product as a dark-yellow viscous oil (48.4 mg, 64%). R\(_f\) = 0.28 (5% MeOH/DCM); IR (film) 3030, 2924, 2853, 1595 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 8.51 (br d, \(J\) = 4.2 Hz, 1H), 8.49-8.46 (br m, 3H), 7.72 (d, \(J\) = 8.4 Hz, 2H), 7.61 (d, \(J\) = 7.8 Hz, 1H), 7.58 (d, \(J\) = 6.0 Hz, 1H), 7.27-7.23 (m, 3H), 4.36 (dd, \(J\) = 7.8, 3.6 Hz, 1H), 3.93 (dd, \(J\) = 11.4,
7.8 Hz, 1H), 3.86 (dd, $J = 11.4, 3.6$ Hz, 1H), 3.70 (s, $J = 2$ Hz), 2.34 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) ppm 150.9, 149.5, 149.1, 148.9, 146.9, 145.1, 135.7, 134.5, 133.5, 130.0, 128.2, 127.2, 123.5, 109.3, 56.0, 55.7, 47.7, 21.6; Exact mass calc'd for C$_{20}$H$_{21}$N$_{4}$O$_{2}$S [M+H]$^+$ 381.1385, found 381.1389.

4-(1-Tosyl-2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-3-yl)thiomorpholine (527i). A vial equipped with a stir bar was charged with potassium iodide (12.5 mg, 75.0 µmol), iodobenzene diacetate (36.2 mg, 113 µmol), 4-methyl-N-(3-vinylpyridin-4-yl)benzenesulfonamide (20.6 mg, 75.0 µmol), and acetonitrile (750 µL). Thiomorpholine (15.1 µL, 150 µmol) was added and the resulting mixture was stirred at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO$_2$, 0.5-1-2-5% methanol in dichloromethane) afforded the desired product as a light-yellow viscous oil (9.60 mg, 34%). $R_f = 0.46$ (5% MeOH/DCM); IR (film) 2922, 2819, 1594 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.45 (br s, 1H), 8.41 (br s, 1H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 5.2$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 4.37 (dd, $J = 9.2$, 3.6 Hz, 1H), 3.95 (dd, $J = 11.6$, 4.0 Hz, 1H), 3.72 (dd, $J = 11.2$, 9.0 Hz, 1H), 2.60-2.41 (m, 8H), 2.40 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) ppm 150.9, 149.7, 147.7, 145.1, 133.7, 130.0, 127.2, 125.4, 108.5, 63.8, 50.6, 50.0, 28.1, 21.6; HRMS (ESI): Exact mass calc'd for C$_{18}$H$_{22}$N$_{3}$O$_{2}$S$_{2}$ [M+H]$^+$ 376.1153, found 376.1135.

$N$-Phenyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-amine (530a). Prepared according to the general procedure using aniline (27.3 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO$_2$, 5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a brown viscous oil (38.2 mg, 70%). $R_f = 0.50$ (50% EtOAc/hexanes); IR (film) 3393, 3288, 3053, 3028, 2925, 2872, 1602, 1503 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.25 (dd, $J = 4.8$, 1.2 Hz, 1H), 7.97 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.25-7.17 (m, 5H), 6.79 (dd, $J = 7.2$, 7.2 Hz, 1H), 6.52 (d, $J = 7.6$ Hz, 1H).
Hz, 2H), 4.84 (dd, J = 7.6, 5.2 Hz, 1H), 4.35 (dd, J = 10.8, 8.0 Hz, 1H), 3.99 (br s, 1H), 3.74 (dd, J = 11.2, 5.6 Hz, 1H), 2.39 (s, 3H); 13C NMR (100 MHz, CDCl3) ppm 152.1, 146.1, 145.2, 144.8, 136.7, 133.3, 130.0, 129.3, 127.3, 123.9, 122.2, 118.7, 113.4, 56.4, 54.3, 21.6; HRMS (ESI): Exact mass calcd for C20H19N3NaO2S [M+Na]+ 388.1096, found 388.1093.

N-(4-(tert-Butyl)phenyl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-amine (530b). Prepared according to the general procedure using 4-tert-butylaniline (47.8 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO2, 5-10-20-40% ethyl acetate in hexanes) afforded the desired product as a dark-brown viscous oil (25.6 mg, 41%, 90% BRSM). Rf = 0.59 (50% EtOAc/hexanes); IR (film) 3391, 3060, 2961, 2867, 1614, 1519 cm−1; 1H NMR (400 MHz, CDCl3) δ 8.24 (d, J = 4.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.26-7.21 (m, 5H), 6.50 (d, J = 8.8 Hz, 2H), 4.82 (dd, J = 7.6, 6.0 Hz, 1H), 4.36 (dd, J = 11.2, 8.0 Hz, 1H), 3.98 (br s, 1H), 3.73 (dd, J = 10.8, 5.6 Hz, 1H), 2.39 (s, 3H), 1.29 (s, 9H); 13C NMR (100 MHz, CDCl3) ppm 152.3, 145.1, 144.8, 143.8, 141.6, 136.6, 133.3, 129.9, 127.3, 126.1, 123.8, 122.0, 113.2, 56.6, 54.6, 33.9, 31.5, 21.6; Exact mass calcd for C24H27N3NaO2S [M+Na]+ 444.1722, found 444.1717.

N-Benzyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-amine (530c). Prepared according to the general procedure using benzylamine (32.8 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO2, 20-40-60-80% ethyl acetate in hexanes) afforded the desired product as a dark yellow viscous oil (50.2 mg, 88%). Rf = 0.34 (50% EtOAc/hexanes); IR (film) 3060, 3026, 2922, 2852, 2338, cm−1; 1H NMR (400 MHz, CDCl3) δ 8.21 (dd, J = 4.8, 1.2 Hz, 1H), 7.91 (dd, J = 8.4, 1.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.33-7.21 (m, 7H), 7.17 (dd, J = 8.0, 4.8 Hz, 1H), 4.25 (dd, J = 8.4, 5.2 Hz, 1H), 4.00 (dd, J = 11.2, 8.4 Hz, 1H), 3.77 (d, J = 4.4 Hz, 2H), 3.70 (dd, J = 10.8, 4.8 Hz, 1H), 2.34 (s, 3H), 1.75 (br s, 1H); 13C NMR (100 MHz, CDCl3) ppm 153.7, 144.8, 144.7, 139.3,
136.5, 133.4, 129.9, 128.4, 128.2, 127.2, 123.3, 121.8, 57.8, 55.3, 51.4, 21.5; HRMS (ESI): Exact mass calcd for C_{21}H_{21}N_{3}NaO_{2}S [M+Na]^+ 402.1252, found 402.1252.

**N-Cyclopentyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-amine (530d).** Prepared according to the general procedure using cyclopentylamine (29.6 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO$_2$, 40-60-80-100% ethyl acetate in hexanes) afforded the desired product as a dark-brown viscous oil (31.7 mg, 59%). R$_f$ = 0.20 (70% EtOAc/hexanes); IR (film) 2954, 2868, 1594 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.19 (dd, $J$ = 4.8, 1.2 Hz, 1H), 7.88 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.68 (d, $J$ = 8.0 Hz, 2H), 7.25 (d, $J$ = 8.0 Hz, 2H), 7.15 (dd, $J$ = 8.4, 4.8 Hz, 1H), 4.26 (dd, $J$ = 8.0, 5.6 Hz, 1H), 4.09 (dd, $J$ = 10.8, 8.0 Hz, 1H), 3.69 (dd, $J$ = 10.8, 5.6 Hz, 1H), 3.20 (ddd, $J$ = 6.8, 6.8, 6.8, Hz, 1H), 2.38 (s, 3H), 1.87-1.73 (m, 3H), 1.72-1.62 (m, 2H), 1.57-1.46 (m, 2H), 1.37-1.19 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 153.1, 144.7, 144.6, 136.5, 133.3, 129.9, 127.3, 123.4, 121.7, 58.4, 57.4, 55.8, 33.2, 32.8, 23.9, 23.7, 21.5; HRMS (ESI): Exact mass calcd for C$_{19}$H$_{23}$N$_{3}$NaO$_{2}$S [M+Na]$^+$ 380.1409, found 380.1415.

**N-Phenethyl-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-amine (530e).** Prepared according to the general procedure using phenethylamine (37.7 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO$_2$, 40-60-80-100% ethyl acetate in hexanes) afforded the desired product as a dark-orange viscous oil (40.4 mg, 68%). R$_f$ = 0.22 (70% EtOAc/hexanes); IR (film) 3060, 3026, 2923, 2853, 1595 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.18 (dd, $J$ = 4.8, 1.2 Hz, 1H), 7.89 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.67 (d, $J$ = 8.4 Hz, 2H), 7.29-7.13 (m, 8H), 4.26 (dd, $J$ = 8.4, 5.2 Hz, 1H), 4.01 (dd, $J$ = 10.8, 8.4 Hz, 1H), 3.70 (dd, $J$ = 11.2, 5.2 Hz, 1H), 2.93-2.88 (m, 1H), 2.82-2.70 (m, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) ppm 153.3, 144.69, 144.66, 139.4, 136.5, 133.4, 129.9, 128.6, 128.5, 127.3, 126.3, 123.3, 121.6, 58.3, 55.1, 48.4, 36.4, 21.5; HRMS (ESI): Exact mass calcd for C$_{22}$H$_{23}$N$_{3}$NaO$_{2}$S [M+Na]$^+$ 416.1409, found 416.1410.
(Piperidin-1-yl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine (530f). Prepared according to the general procedure using piperidine (29.6 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO₂, 40-60-80-100% ethyl acetate in hexanes) afforded the desired product as a brown viscous oil (33.7 mg, 63%). R_f = 0.12 (50% EtOAc/hexanes); IR (film) 2933, 2853, 1595 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 8.4, 4.8 Hz, 1H), 4.31 (dd, J = 9.2, 3.6 Hz, 1H), 4.03 (dd, J = 12.0, 3.6 Hz, 1H), 3.76 (dd, J = 11.6, 9.6 Hz, 1H), 2.51 (br dd, J = 5.2, 5.2 Hz, 2H), 2.37 (s, 3H), 2.19 (br m, 2H), 1.50 (br d, J = 4.8 Hz, 4H), 1.35 (br dd, J = 5.6, 5.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) ppm 150.8, 144.8, 144.6, 137.5, 133.3, 129.9, 127.3, 123.4, 120.9, 64.6, 49.6, 49.5, 25.5, 23.9, 21.5; Exact mass calcd for C₁₉H₂₃N₃NaO₂S [M+Na]+ 380.1409, found 380.1395.

Ethyl 1-(1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)piperidine-4-carboxylate (530g). Prepared according to the general procedure using ethyl isonipecotate (46.2 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO₂, 40-60-80-100% ethyl acetate in hexanes) afforded the desired product as light-brown viscous oil (45.5 mg, 71%). R_f = 0.17 (50% EtOAc/hexanes); IR (film) 2947, 2815, 1728, 1592 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.23 (dd, J = 5.4, 1.8 Hz, 1H), 7.93 (dd, J = 8.4, 1.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.17 (dd, J = 8.4, 4.8 Hz, 1H), 4.27 (dd, J = 9.6, 4.2 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.90 (dd, J = 11.4, 3.6 Hz, 1H), 3.76 (dd, J = 11.4, 9.6 Hz, 1H), 2.57 (br d, J = 10.8 Hz, 1H), 2.50 (br d, J = 11.4 Hz, 1H), 2.41-2.36 (m, 1H), 2.38 (s, 3H), 2.16-2.11 (m, 1H), 1.89 (dd, J = 10.8, 9.0 Hz, 1H), 1.74 (ddd, J = 14.4, 14.4, 1.8 Hz, 2H), 1.68-1.58 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) ppm 174.8, 151.4, 144.8, 144.6, 137.3, 133.3, 129.9, 127.2, 123.3, 121.0, 64.2, 60.2, 49.8, 48.4
Ethyl 4-(1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)piperazine-1-carboxylate (530h). Prepared according to the general procedure using ethyl 1-piperazinecarboxylate (44.0 µL, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO₂, 50-75-100% ethyl acetate in hexanes) afforded the desired product as an orange viscous oil (55.6 mg, 86%). $R_f = 0.10$ (50% EtOAc/hexanes); IR (film) 3062, 2981, 2927, 2861, 1696, 1594 cm⁻¹; $^1$H NMR (400 MHz, CDCl₃) δ 8.24 (dd, $J = 4.8, 1.2$ Hz, 1H), 7.95 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 7.6$ Hz, 2H), 7.18 (dd, $J = 8.0, 4.8$ Hz, 1H), 4.30 (dd, $J = 9.2, 3.6$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.90 (dd, $J = 12.0, 4.0$ Hz, 1H), 3.77 (dd, $J = 11.2, 9.2$ Hz, 1H), 3.35 (br s, 4H), 2.42 (br s, 2H), 2.39 (s, 3H), 2.19-2.11 (br m, 2H), 1.22 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) ppm 155.2, 150.6, 144.9, 144.7, 137.4, 133.2, 129.9, 127.2, 123.6, 121.1, 64.1, 61.3, 49.5, 48.1 (br), 43.4 (br), 21.5, 14.6; Exact mass calcd for C₂₁H₂₆N₄NaO₄S [M+Na]+ 453.1572, found 453.1574.

**tert-Butyl 4-(1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)piperazine-1-carboxylateamine (530i).** Prepared according to the general procedure using tert-butyl piperazine-1-carboxylate (55.9 mg, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO₂, 20-40-60-80% ethyl acetate in hexanes) afforded the desired product as a golden viscous oil (50.8 mg, 74%). $R_f = 0.15$ (50% EtOAc/hexanes); IR (film) 3384, 3062, 2975, 2930, 2860, 1692, 1591 cm⁻¹; $^1$H NMR (600 MHz, CDCl₃) δ 8.24 (dd, $J = 4.8, 1.2$ Hz, 1H), 7.94 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 7.18 (dd, $J = 8.4, 4.8$ Hz, 1H), 4.29 (dd, $J = 9.0, 3.6$ Hz, 1H), 3.90 (dd, $J = 11.4, 4.2$ Hz, 1H), 3.77 (dd, $J = 12.0, 9.6$ Hz, 1H), 3.29 (br s, 4H), 2.39
(br s, 2H), 2.39 (s, 3H), 2.14 (br s, 2H), 1.42 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) ppm 154.5, 150.8, 144.9, 144.7, 137.4, 133.2, 129.9, 127.2, 123.5, 121.1, 79.6, 64.1, 49.6, 48.2 (br), 44.0 (br, 0.5C), 42.9 (br, 0.5C), 28.4, 21.5; Exact mass calcd for C$_{23}$H$_{30}$N$_4$O$_4$S $[M+Na]^+$ 481.1885, found 481.1903.

**(E)-3-(4-Cinnamylpiperazin-1-yl)-1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridine** (530j). Prepared according to the general procedure using trans-1-cinnamylpiperazine (60.7 mg, 300 µmol) and 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol). Flash column chromatography of the residue (SiO$_2$, 0.5-1-2-5-10% methanol in dichloromethane) afforded the desired product as a light-yellow viscous oil (46.7 mg, 66%). R$_f$ = 0.42 (5% MeOH/DCM); IR (film) 3026, 2935, 2812, 1673, 1595 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.23 (dd, $J = 4.8$, 1.2 Hz, 1H), 7.93 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.39-7.20 (m, 7H), 7.16 (dd, $J = 8.4$, 5.4 Hz, 1H), 6.49 (d, $J = 15.6$ Hz, 1H), 6.22 (ddd, $J = 15.0$, 6.6, 6.6 Hz, 1H), 4.31 (dd, $J = 9.0$, 3.6 Hz, 1H), 3.96 (dd, $J = 11.4$, 4.2 Hz, 1H), 3.76 (dd, $J = 11.4$, 9.6 Hz, 1H), 3.13 (br s, 2H), 2.61-2.56 (br m, 2H), 2.53-2.38 (br m, 4H), 2.34 (s, 3H), 2.32-2.26 (br m, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$) ppm 151.1, 144.74, 144.68, 137.3, 136.7, 133.3, 129.9, 128.5, 127.6, 127.3, 126.3, 123.3, 120.9, 63.9, 60.8, 52.9, 49.3, 48.0, 21.5; HRMS (ESI): Exact mass calcd for C$_{27}$H$_{31}$N$_4$O$_2$S $[M+H]^+$ 475.2168, found 475.2146.

**Methyl 2-((1-tosyl-2,3-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)amino)acetate** (530k). A vial equipped with a stir bar was charged with potassium iodide (24.9 mg, 150 µmol), iodobenzene diacetate (72.5 mg, 225 µmol), 4-methyl-N-(2-vinylpyridin-3-yl)benzenesulfonamide (41.2 mg, 150 µmol), and acetonitrile (1.5 mL). Potassium carbonate (41.5 mg, 300 µmol) and glycine methyl ester hydrochloride (37.7 mg, 300 µmol) were added and the resulting mixture was stirred...
at rt for 18 h. The reaction mixture was then diluted with ethyl acetate and concentrated. Flash column chromatography of the residue (SiO₂, 50-80-100% ethyl acetate in hexanes) afforded the desired product as an orange viscous oil (33.9 mg, 63%). R_f = 0.18 (70% EtOAc/hexanes); IR (film) 3327, 3062, 2951, 2924, 1741, 1594 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, J = 4.8, 1.2 Hz, 1H), 7.90 (dd, J = 8.4, 1.2 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.17 (dd, J = 8.4, 5.2 Hz, 1H), 4.25 (dd, J = 8.4, 5.2 Hz, 1H), 4.03 (dd, J = 10.8, 8.4 Hz, 1H), 3.70 (s, 3H), 3.68 (dd, J = 10.8, 4.8 Hz, 1H), 3.46 (s, 2H), 2.38 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) ppm 172.1, 153.1, 144.8, 144.7, 136.4, 133.2, 129.9, 127.3, 123.5, 121.6, 57.5, 55.1, 51.9, 48.1, 21.5; Exact mass calcd for C₁₇H₁₉N₃NaO₄S [M+Na]⁺ 384.0994, found 384.0976.

**Ethyl 1-cyanocyclopent-3-enecarboxylate (569).**²⁵⁷ To a flame dried flask equipped with a stir bar was added K₂CO₃ (11.1 g, 80.0 mmol), ethyl cyanoacetate (2.13 mL, 20.0 mmol), and DMF (20 mL). The resulting mixture was stirred at room temperature followed by the dropwise addition of the dichlorobutene (3.16 mL, 30.0 mmol) in DMF (6 mL). After stirring for 15 hours at room temperature, the reaction mixture was diluted with water and extracted with ether. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated. Flash column chromatography of the residue (SiO₂, 5-20% ethyl acetate in hexanes) afforded the desired product as a clear liquid (3.26 g, 99%). R_f = 0.25 (10% EtOAc/hexanes); IR (film) 2986, 2939, 2863, 2245, 1743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.67 (s, 2H), 4.25 (q, J = 5.6 Hz, 2H), 3.11 (d, J = 12.4 Hz, 2H), 3.02 (d, J = 12.4 Hz, 2H), 1.31 (t, J = 5.6 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 169.0, 127.3, 121.0, 62.9, 45.3, 43.8, 13.8; HRMS (ESI) Exact mass calcd for C₉H₁₂NO₂ [M+H]⁺ 166.0863, found 166.0869.

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Cyclopent-3-enecarbonitrile (565). To a flask equipped with a stir bar was added the carboxylate (9.40 g, 56.9 mmol), NaCl (13.3 g, 228 mmol), and DMSO (86 mL) and the resulting suspension was heated to 150 °C for 19 h. The reaction mixture was then cooled to room temperature, diluted with water, and extracted with ether. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated. Vacuum distillation of the crude oil afforded the desired carbonitrile as a clear oil (2.32 g, 44%). The characterization of this compound matched that of literature.²⁵⁷

Methyl 4-(1-cyanocyclopent-3-en-1-yl)nicotinate (560). To a flame dried flask equipped with a stir bar was added the methyl nicotinate (1.37 g, 8.00 mmol) and the carbonitrile (497 mg, 5.33 mmol). A condenser was attached, KHMDS (1 M in THF) (8 mL) was added through the condenser, and the resulting mixture was stirred under reflux for 16 hours. The reaction mixture was then cooled to room temperature, poured onto water and extracted with ether. The organic extracts were washed with satd aq NaHCO₃, water, and brine, dried (MgSO₄), and concentrated. Flash column chromatography of the residue (SiO₂, 0.5-2% methanol in dichloromethane) afforded the desired product as a golden-orange viscous oil (515 mg, 42%). Rᵣ = 0.65 (5% MeOH/DCM); IR (film) 3440, 3063, 2952, 2857, 2237, 1728, 1586 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.70 (d, J = 5.2 Hz, 1H), 7.30 (d, J = 5.2 Hz, 1H), 5.82 (s, 2H), 4.00 (s, 3H), 3.36 (d, J = 15.6 Hz, 2H), 3.13 (d, J = 15.2 Hz, 2H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 166.9, 152.6, 151.4, 147.9, 128.1, 126.5, 123.3, 121.0, 52.9, 46.9, 43.6; HRMS (ESI) Exact mass calcd for C₁₃H₁₃N₂O₂ [M+H]⁺ 229.0977, found 229.0972.

4-(1-Cyanocyclopent-3-en-1-yl)nicotinic acid (571). To a flask equipped with a stir bar was added the ester (79.0 mg, 346 µmol) and ethanol (6.92 mL). To the solution was added NaOH (138
mg, 3.46 mmol) in water (1.73 mL), and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was acidified to a pH of 2 with 1 M HCl and concentrated to remove ethanol. The residue was diluted with water, extracted with dichloromethane, and the organic extracts were dried (MgSO₄) and concentrated. Flash column chromatography of the residue (SiO₂, 1-5% methanol in dichloromethane) afforded the desired product as a white viscous oil (12.6 mg, 17%). Rf = 0.62 (5% MeOH/DCM); IR (film) 2986, 2918, 2698, 1701, 1602 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, 1H), 8.80 (d, J = 5.2 Hz, 1H), 8.24 (br s, 1H), 7.37 (d, J = 5.6 Hz, 1H), 5.86 (s, 2H), 3.40 (d, J = 14.0 Hz, 2H), 2.77 (d, J = 14.0 Hz, 2H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 176.0, 163.0, 155.6, 155.0, 150.1, 128.5, 119.1, 118.3, 50.8, 50.0; (ESI) Exact mass calcd for C₁₂H₁₁N₂O₂ [M+H]⁺ 215.0821, found 215.0812.

3'-Imino-2',3'-dihydro-1'H-spirocyclopent[3]ene-1,4'-isoquinolin]-1'-one (574). To a flame dried flask equipped with a stir bar was added the benzoate (573 µL, 4.00 mmol) and the carbonitrile (248 mg, 2.67 mmol). A condenser was attached, KHMDS (4 mL, 1 M in THF) was added through the condenser, and the resulting mixture was stirred under reflux for 16 hours. The reaction mixture was then cooled to room temperature, poured onto water and extracted with ether. The organic extracts were washed with satd aq NaHCO₃, water, and brine, dried (MgSO₄), and concentrated. Flash column chromatography of the residue (SiO₂, 1-2-5-10-20% methanol in dichloromethane) afforded the isoquinolinone as an off-white viscous oil (22.3 mg, 4%). Rf = 0.22 (5% MeOH/DCM); IR (film) 3272, 3005, 1631, 1599, 1509 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (dd, J = 7.6, 0.8 Hz, 1H), 7.58 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H), 7.39 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 5.94 (s, 2H), 3.24 (d, J = 14.8 Hz, 2H), 2.98 (d, J = 14.8 Hz, 2H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 168.3, 147.2, 133.6, 129.6, 127.4, 127.0, 125.0, 124.5, 52.8, 45.9; (ESI) Exact mass calcd for C₁₃H₁₃N₂O [M+H]⁺ 213.1022, found 213.1019.
1'H-Spiro[cyclopent[3]ene-1,4'-isoquinoline]-1',3'(2'H)-dione (575). To a flask equipped with a stir bar was added the isoquinolinone (22.3 mg, 98.1 µmol) and methanol (1.96 mL). To the solution was added NaOH (4.70 mg, 118 µmol) in water (491 µL), and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was acidified to a pH of 2 with 1 M HCl and concentrated to remove methanol. The residue was diluted with water, extracted with dichloromethane, and the organic extracts were dried (MgSO₄) and concentrated to afford the isoquinolinedione as a white solid (18.3 mg, 88%). Mp 152.0-156.0 °C; R_f = 0.63 (5% MeOH/DCM); IR (film) 3192, 3079, 2921, 2847, 1708, 1689 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.54 (br s, 1H), 8.18 (dd, J = 8.4, 1.6 Hz, 1H), 7.63 (ddd, J = 9.2, 7.6, 1.2 Hz, 1H), 7.43 (m, 2H), 5.84 (s, 2H), 3.38 (d, J = 13.6 Hz, 2H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 177.6, 164.2, 147.9, 135.2, 128.5, 127.9, 127.4, 125.0, 122.5, 122.5, 51.0, 50.7; (ESI) Exact mass calcd for C₁₃H₁₂NO₂ [M+H]+ 214.0869, found 214.0834.

1-Cyanocyclopent-3-enecarboxylic acid (576). To a flask equipped with a stir bar was added the cyano carboxylate (1.00 g, 6.05 mmol) and ethanol (121 mL). To the solution was added NaOH (291 mg, 7.26 mmol) in water (30 mL) and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then acidified to a pH of 2 with 1 M HCl and concentrated. The residue was diluted with water, extracted with dichloromethane and the organic extracts were dried (MgSO₄) and concentrated to afford the desired acid as an off-white crystalline solid (659 mg, 79%). Mp 68.0-72.0 °C; R_f = 0.15 (5% MeOH/DCM); IR (film) 3488, 2929, 2604, 2250, 1730, 1629 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.0 (br s, 1H), 5.72 (s, 1H); 3.16 (m, 4H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 174.5, 127.4, 120.3, 45.1, 44.0; (ESI) Exact mass calcd for C₇H₈NO₂ [M+H]+ 137.0471, found 137.0473.
(1R,4S,6R)-6-Iodo-3-oxo-2-oxabicyclo[2.2.1]heptane-4-carbonitrile (577). To a flame dried vial equipped with a stir bar was added 6(MeO)StilbPBAM (3.30 mg, 5.00 µmol), the carboxylic acid (13.7 mg, 100 µmol) and toluene (2 mL), and the reaction was cooled to -20 °C. NIS (23.4 mg, 104 µmol) was added and the reaction mixture was stirred without light for 24 h. The mixture was treated with 20% aq sodium thiosulfate (2 mL) and then partitioned between dichloromethane (15 mL) and 3 M NaOH (15 mL). The aqueous layer was extracted twice and the organic layers were combined, dried (MgSO₄), and concentrated. Flash column chromatography (SiO₂, 5-10-20% ethyl acetate in hexanes) yielded the desired lactone as a light-yellow solid (6.3 mg, 24%). The product was determined to be 32% ee by chiral HPLC analysis (Chiralcel OD-H, 10% iPrOH/hexanes, 1 mL/min, t₁(ε₁, minor) = 26.7 min, t₁(ε₂, major) = 31.7 min). Mp 163.0-165.0 °C; [α]D²⁰ 0 - no optical rotation taken due to low ee; Rf = 0.74 (50% EtOAc/hexanes); IR (film) 3014, 2962, 2920, 2254, 1780 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.03 (d, J = 1.6 Hz, 1H), 4.15 (dddd, J = 7.2, 4.0, 2.0, 0.8 Hz, 1H), 3.00 (ddd, J = 14.4, 8.0, 2.0 Hz, 1H), 2.97 (d, J = 11.2 Hz, 1H), 2.77 (ddd, J = 6.8, 2.4, 2.4 Hz, 1H), 2.74 (dd, J = 14.0, 4.4 Hz, 1H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 168.4, 113.8, 84.3, 44.2, 41.2, 40.5, 12.3; (ESI) Exact mass calcd for C₇H₇INO₂ [M+H]+ 263.9516, found 263.9508.

(1R,4S,6R)-6-Bromo-3-oxo-2-oxabicyclo[2.2.1]heptane-4-carbonitrile (580). To a flame dried vial equipped with a stir bar was added DMAP (9.80 mg, 80.0 µmol), the carboxylic acid (54.9 mg, 400 µmol) and dichloromethane (4 mL). NIS (23.4 mg, 104 µmol) was added and the reaction mixture was stirred at room temperature without light for 12 h. The mixture was treated with 20% aq sodium thiosulfate (4 mL) and then partitioned between dichloromethane (30 mL) and 3 M NaOH (30 mL). The aqueous layer was extracted twice and the organic layers were combined, dried (MgSO₄), and concentrated. Flash column chromatography (SiO₂, 5-10-20% ethyl acetate in hexanes) yielded the desired lactone as an off-white solid (16.8 mg, 19%). Mp 162.0-164.0 °C; Rf = 0.74 (50% EtOAc/hexanes); IR (film) 2922, 2255, 1787 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ
4.98 (d, $J = 0.8$ Hz, 1H), 4.22 (dddd, $J = 7.6, 3.2, 1.6, 1.2$ Hz, 1H), 2.96 (ddd, $J = 14.4, 7.6, 2.0$ Hz, 1H), 2.85 (d, $J = 11.2$ Hz, 1H), 2.73 (ddd, $J = 11.2, 2.0, 2.0$ Hz, 1H), 2.65 (dd, $J = 14.4, 4.0$ Hz, 1H); $^{13}$C NMR (125.8 MHz, CDCl$_3$) ppm 168.2, 113.9, 82.6, 43.1, 41.0, 40.1, 39.7; (ESI) Exact mass calcd for C$_7$H$_7$BrNO$_2$ [M+H]$^+$ 215.9655, found 215.9658.

(1R,4S,6R)-3-Oxo-6-(phenylselanyl)-2-oxabicyclo[2.2.1]heptane-4-carbonitrile (582). To a flame dried vial equipped with a stir bar was added PBAM (2.50 mg, 5.00 µmol), the carboxylic acid (13.7 mg, 100 µmol) and toluene (2 mL). NIS (23.4 mg, 104 µmol) was added and the reaction mixture was stirred without light for 24 h at rt. The mixture was treated with 20% aq sodium thiosulfate (2 mL) and then partitioned between dichloromethane (15 mL) and 3 M NaOH (15 mL). The aqueous layer was extracted twice and the organic layers were combined, dried (MgSO$_4$), and concentrated. Flash column chromatography of the residue (SiO$_2$, 5-10% ethyl acetate in hexanes) yielded the desired lactone as a tan solid (7.6 mg, 26%). The product was determined to be 2% ee by chiral HPLC analysis (Chiralcel OD-H, 10% tBuOH/hexanes, 1 mL/min, $t_e(e_1$, minor) = 28.7 min, $t_e(e_2$, major) = 38.9 min). Mp 87.0-91.0 °C; [$\alpha$]$^D_{20}$ - no optical rotation taken since compound was nearly racemic. $R_f = 0.48$ (50% EtOAc/hexanes); IR (film) 2922, 2852, 2253, 1799 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57 (d, $J = 6.8$ Hz, 2H), 7.36 (m, 3H), 4.77 (s, 1H), 3.64 (dd, 7.2, 7.2 Hz, 1H), 2.73 (ddd, $J = 14.0, 8.4, 1.2$ Hz, 1H), 2.63 (m, 2H), 2.19 (dd, $J = 13.6, 4.8$ Hz, 1H); $^{13}$C NMR (125.8 MHz, CDCl$_3$) ppm 169.0, 134.5, 129.8, 129.0, 127.5, 114.6, 83.0, 43.2, 41.6, 38.8, 35.7; (ESI) Exact mass calcd for C$_{13}$H$_{11}$NNaO$_2$Se [M+H]$^+$ 315.9853, found 315.9848.

1-Cyanocyclopent-3-enecarbonyl chloride (584). To a flask equipped with a stir bar was added the carboxylic acid (500 mg, 3.65 mmol) and SOCl$_2$ (7.90 mL, 0.109 mol). The resulting mixture was stirred under reflux for 18 h before being cooled to rt and concentrated. The resulting residue was carried onto the next step quantitatively without any further purification.
1-(2-Diazoacetyl)cyclopent-3-enecarbonitrile (585). To a flask equipped with a stir bar was added the acid chloride (794 mg, 5.10 mmol). The flask was chilled to 0 °C followed by the addition of CH₂N₂ (35.7 mmol, 1.50 g) in Et₂O and the resulting mixture was warmed to rt and allowed to stir for 18 h. The reaction mixture was then diluted with EtOAc and washed with satd aq NaHCO₃, satd aq NH₄Cl, and brine. The organic layer was dried (MgSO₄), filtered, and concentrated. Flash column chromatography of the residue (SiO₂, 1-2-5-10-20-50% ethyl acetate in hexanes) afforded the desired diazoketone as a non-viscous yellow oil (316 mg, 38%). Rᵣ = 0.60 (50% EtOAc/hexanes); IR (film) 3109, 2925, 2856, 2236, 2118, 1641 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.89 (s, 1H), 5.68 (s, 2H), 3.12 (d, J = 15.2 Hz, 2H), 2.96 (d, J = 14.8 Hz, 2H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 188.0, 127.4, 122.3, 54.6, 48.7, 43.7; (ESI) Exact mass calcd for C₈H₇N₃O [M⁺] 161.0584, found 161.0589.

Methyl 2-(1-cyanocyclopent-3-en-1-yl)acetate (586). To a flame-dried flask equipped with a stir bar and wrapped in aluminum foil was added the diazoketone (154 mg, 956 µmol), MeOH (19.3 mL) and anhydrous THF (13.4 mL). The reaction mixture was chilled to -20 °C before a solution of silver benzoate (48.1 mg, 210 µmol) in freshly distilled Et₃N (770 µL, 5.52 mmol) was added. The resulting mixture was warmed to rt and allowed to stir for 6 h. The solvents were evaporated and the residue was taken up in EtOAc. The organic layer was washed with satd aq solutions of NaHCO₃, NH₄Cl and brine, dried (MgSO₄), filtered and concentrated to afford clean product as an orange-brown oil (102 mg, 64%). Rᵣ = 0.27 (20% EtOAc/hexanes); IR (film) 2921, 2852, 2237, 1739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.69 (s, 2H), 3.75 (s, 3H), 3.03 (d, J = 14.8 Hz, 2H), 2.71 (s, 2H), 2.62 (d, J = 14.8 Hz, 2H); ¹³C NMR (125.8 MHz, CDCl₃) ppm 169.8, 127.4, 122.3, 54.6, 48.7, 43.7; (ESI) Exact mass calcd for C₉H₁₁NO₂ [M⁺] 165.0784, found 165.0785.
1-Cyanocyclopent-3-enecarboxylic acid (583). To a flask equipped with a stir bar was added the ester (18.7 mg, 113 µmol) and methanol (2.3 mL). To the solution was added NaOH (5.40 mg, 136 µmol) in water (565 µL) and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then acidified to a pH of 2 with 1 M HCl and concentrated. The residue was diluted with water, extracted with dichloromethane and the organic extracts were dried (MgSO$_4$) and concentrated to afford the desired acid as a light-yellow viscous oil (15.1 mg, 88%). $R_f = 0.31$ (5% MeOH/DCM); IR (film) 3473, 3068, 2925, 2859, 2241, 1718 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.13 (br s, 1H), 5.69 (s, 2H), 3.03 (d, $J = 15.2$ Hz, 2H), 2.78 (s, 2H), 2.62 (d, $J = 14.8$ Hz, 2H); $^{13}$C NMR (125.8 MHz, CDCl$_3$) ppm 175.3, 127.9, 124.1, 44.5, 41.9, 36.9; Exact mass calcd for C$_8$H$_9$NO$_2$ [M+] 151.0628, found 151.0632.

(1R,5S,7R)-7-Iodo-3-oxo-2-oxabicyclo[3.2.1]octane-5-carbonitrilecarbonitrile (587). To a flame dried vial equipped with a stir bar was added PBAM (1.00 mg, 2.10 µmol), the carboxylic acid (6.20 mg, 41.0 µmol) and toluene (820 µL). NIS (9.60 mg, 42.7 µmol) was added and the reaction mixture was stirred at rt without light for 24 h. The mixture was treated with 20% aq sodium thiosulfate (2 mL) and then partitioned between dichloromethane (7 mL) and 3 M NaOH (7 mL). The aqueous layer was extracted twice and the organic layers were combined, dried (MgSO$_4$), and concentrated. Flash column chromatography (SiO$_2$, 5-10-20% ethyl acetate in hexanes) yielded the desired lactone as an off-white solid (1.3 mg, 12%). The product was determined to be 4% ee by chiral HPLC analysis (Chiralpak IB, 10% iPrOH/hexanes, 1 mL/min, $t_r(e_1$, major) = 47.5 min, $t_r(e_2$, minor) = 55.8 min). $[\alpha]_{D}^{20}$ - no optical rotation taken since compound was nearly racemic; $R_f = 0.24$ (20% EtOAc/hexanes); IR (film) 3464, 2920, 2245, 1741 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.04 (d, $J = 2.4$ Hz, 1H), 4.45 (dddd, $J = 8.0, 8.0, 4.4, 2.4$ Hz, 1H), 3.04 (dd, $J = 18.4, 2.8$ Hz, 1H), 3.02 (dd, $J = 15.6, 1.6$ Hz, 1H), 2.96 (dddd, $J = 13.2, 2.8, 2.8$ Hz, 1H), 2.90-2.82 (m, 2H), 2.43 (d, $J = 13.2$ Hz, 1H); $^{13}$C NMR (125.8 MHz, CDCl$_3$) ppm 164.1, 119.2, 86.5, 48.2, 42.6, 36.3, 35.4, 17.5; Exact mass calcd for C$_8$H$_9$INO$_2$ [M+H]$^+$ 277.9672, found 277.9668.
(1R,4S,6R)-6-Iodo-4-phenyl-2-oxabicyclo[2.2.1]heptan-3-one (596). To a vial equipped with a stir bar was added StilbPBAM (6.00 mg, 10.0 µmol), the carboxylic acid (18.8 mg, 100 µmol) and toluene (2 mL), and the reaction was cooled to -20 °C. NIS (23.4 mg, 104 µmol) was added and the reaction mixture was stirred without light for 24 h. The mixture was treated with 20% aq sodium thiosulfate (2 mL) and then partitioned between dichloromethane (15 mL) and 6 M NaOH (15 mL). The aqueous layer was extracted twice and the organic layers were combined, dried (MgSO₄), and concentrated. Flash column chromatography (SiO₂, 10% ethyl acetate in hexanes) yielded the desired lactone as a light-yellow solid (9.4 mg, 30%). The product was determined to be 65% ee by chiral HPLC analysis (Chiralpak IA, 10% iPrOH/hexanes, 1 mL/min, t(e₁, minor) = 8.8 min, t(e₂, major) = 12.8 min). Mp 54.0-56.0 °C; [α]D²⁰ -89.0 (c 0.30, CHCl₃); Rᵣ = 0.36 (10% EtOAc/hexanes); IR (film) 3030, 2927, 2860, 1786 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.43-7.34 (m, 5H), 5.05 (d, J = 1.2 Hz, 1H), 4.28 (ddd, J = 6.6, 4.2, 2.4 Hz, 1H), 2.97 (ddd, J = 13.8, 7.8, 1.8 Hz, 1H), 2.90 (d, J = 10.8, 1H), 2.72 (dddd, J = 4.2, 2.4, 2.4, 2.4 Hz, 1H), 2.62 (dd, J = 13.8, 4.2 Hz, 1H); ¹³C NMR (150.9 MHz, CDCl₃) ppm 176.0, 134.0, 128.7, 128.2, 127.2, 83.3, 56.2, 42.9, 41.1, 16.8; Exact mass calcd for C₁₂H₁₂IO₂ [M+H]⁺ 314.9876, found 314.9872.