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Intercepting Photochemically Generated Aminoalkyl and Aryl Radical Intermediates to Access Complexity Quickly

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B.S., Hope College, 2016

Advisor: Nathan T. Jui, Ph.D.

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By: Cameron J. Pratt

By using radicals generated by photoredox catalysts, three carbon to carbon bond forming reactions have been developed. These methods are robust and operate under mild conditions. The first method showcases a simple and scalable approach to synthesizing a large range of unnatural amino acids which could modulate cell permeability and in vivo stability. A key discovery in this process was the significant effect amine loading had on restricting product formation to the desired mono-functionalized products. This method was also shown to work in increasingly complex amines including on the active ingredient of cough medicine: dextromethorphan. Using a similar redox neutral mechanistic pathway, the second method showcases a unique way to install cyclobutanes on a carbon alpha to the nitrogen in tertiary anilines. These cyclobutanes, which are often difficult to install, can act as phenyl ring isosteres. In this case, a breakthrough was made with the electrophilic strain-releasing coupling partner. It was found that electron poor rings in the phenyl sulfone led to the desired reactivity. The final chapter highlights how spirocyclic compounds can be formed via a radical hydroarylation pathway that is a metal-free alternative to existing radical methods. Access to these types of scaffolds is already valuable thanks to their presence in a wide selection of biologically relevant molecules. Overcoming the need for a metal photoredox catalyst was achieved by using a cyanoarene catalyst.

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Chapter 1:

Light: A Historic Reagent

Figure 1.1 View from Point Lobos State Natural Reserve taken during the ninth Pacific Symposium on Radical Chemistry

1.1 Light and Life

For billions of years, life on this planet has maintained an intimate relationship with light. To find evidence for this statement, all one needs to do is look up. The oxygen in the troposphere which organic life has breathed for eons serves as a reminder of the long-running partnership plants forged with light long ago. Further up in stratosphere, the photolysis of dioxygen via solar radiation equipped our world with the ozone layer that protects organisms from the more dangerous ends of the electromagnetic spectrum. Even the beauty of the auroras (northern lights) in the mesosphere are a result of light-induced excitations and ionizations events. Photochemistry is essentially the source of life and as such is not new or novel by any universal standard. The interactions of physical materials and light which alters chemical structures has been occurring quietly without humankind's intervention or knowledge for aeons.[1]

Our own human history is intricately connected with light. The physical properties of light are on display all around us and serve as the bedrock for communication via reading and writing. Indeed, the white space that lines these black symbols show how light is constantly being absorbed and reflected. Beyond just the light reflecting off this page, a chemical isomerization reaction is also occurring for the sense of sight to be achieved. Deep in the eye, different pairs of proteins and retinal molecules react sending signals to the brain that piece together an image bursting with color and depth. Granted, uncovering the chemical basis for sight is a more recent accomplishment for humankind. In fact, it has taken a great deal of time and effort to untangle the physical nature of light from its potential as a source for chemical reactivity.

Light and life as we know it is impossible to separate. But light alone is not the sole source of innovation, merely a key ingredient. It is up to the organism to find how chemical reactions can be driven forward to productive ends using the absorption of ultraviolet, visible, or infrared radiation. In this work you will find three methods that are rooted in using light as an energy source

– instead of hazardous reagents or harsh conditions – to selectively forge carbon to carbon bonds. A particular focus on drug-like molecules is present to ground the work in practical applications that once again prove how light, and life are intertwined.

1.2 Brief History of Photochemistry

In the early seventeen hundred, alchemists had begun to untangle and report on the ability of light to generate thermal energy. Distillation of spirits could be achieved without fire.[2] Combustion reactions could be started by focusing the sun's rays via "burning mirrors" (lens) onto substances, raising their temperature above the threshold of spontaneous igintion.[3] Later in the eighteenth century, Joseph Priestley noted that light could be used for more than just thermal energy. His study on "different kinds of airs" allowed him to stumble upon the remarkable discovery that that air in which a candle had burned out in could, after being exposed to a sprig of mint and light, support a new lit candle.[4] Effectively, Priestley found that carbon dioxide could be converted to oxygen… an essential portion of photosynthesis.

Another key leap forward for the field of photochemistry was achieved by Johann Wolfgang Döbereine in 1831. Naturally, chemical yields are an important result for any reaction but for the photochemist, the quantum yield must also be considered. This yield is a measurement of the number of product forming events that occur per photon of light applied to the reaction setup. This yield is important for studying the efficiency of a catalyst or proposing radiation-induced chain reactions (which would possibly give quantum yields greater that 1). To study this yield, chemists use chemical actinometers which react in the presence of light producing some easily identified reaction product. Döbereine detailed the first example of a chemical actinometer in his work on the decomposition of iron(III)oxide in oxalic acid to basic iron(II)oxide and carbon dioxide in the presence of sunlight.[5] This is also an early example of a light induced metal redox reaction (photoredox reaction).

Further discoveries in photoinduced Diels-Alder reactions, cyclo-additions, dimerization reactions, and olefin isomerizations provided proof of the sun's ability to drive a multitude of chemical reactions.[1] Discovering that these reactions resulted from some excited state of a molecule required further study and the development of a clearer description of the paths followed in each reaction. To this end, it was the study of phosphorescence and multiform emission that led to development of the Jabloński state diagram and the important theory of the "triplet state". In short, it was proposed that for a molecule to be able to emit multiple longer wavelengths after absorbing a singular wavelength, there must be at least one semi-stable energy level that exists at a lower energy level than the level that would exist immediately following absorption. These levels were further separated by the spin of electron and excited vs. ground state as shown in Figure 1.2. Phosphorescence is typically long lived due to relaxation requiring a spin-forbidden relaxation step. Most photochemical reactions are reacting from this long-lived state. To access this state reliably, ultraviolet light was used to access the triplet state through the singlet excited state present in small pi-systems. It was not until the development of singlet and triplet sensitizers that this requirement of ultraviolet light was negated.[6] These sensitizers serve as the starting point for photoredox method development.

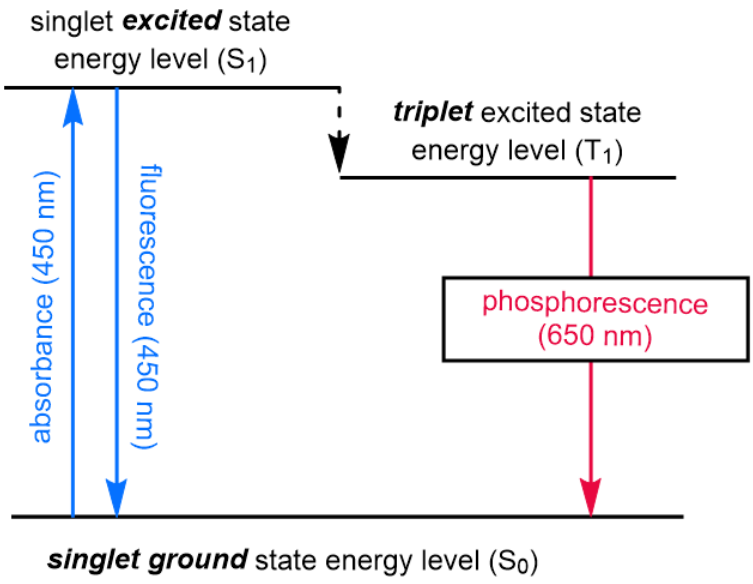

Figure 1.2. State diagram proposed by Jabloński to explain phosphorescence. Dotted line indicates intersystem crossing that may occur after singlet ground state is excited.

1.3 Introduction to Photoredox Catalysis

Sensitizers (or in this work photoredox catalysts) can be transition metal complexes or metal free organic dyes. The mechanism of catalysis for photoredox can involve energy or electron transfer once excited. Simple energy transfer is possible through the Förster resonance energy transfer mechanism. In this case, a sensitizer that is excited can radiate energy at either the same wavelength or a higher wavelength to another molecule (exciting it). No electron is transferred, and no polar intermediates are formed (Figure 1.3a).[7] Direct energy transfer via electrons is possible through the Dexter electron transfer mechanism. Here, the excited electron in the sensitizer's triplet state is directly transferred into an acceptor molecule, while at the same time the acceptor molecule donates an electron back into the singly occupied molecular orbital (SOMO) of the sensitizer (Figure 1.3b). Once

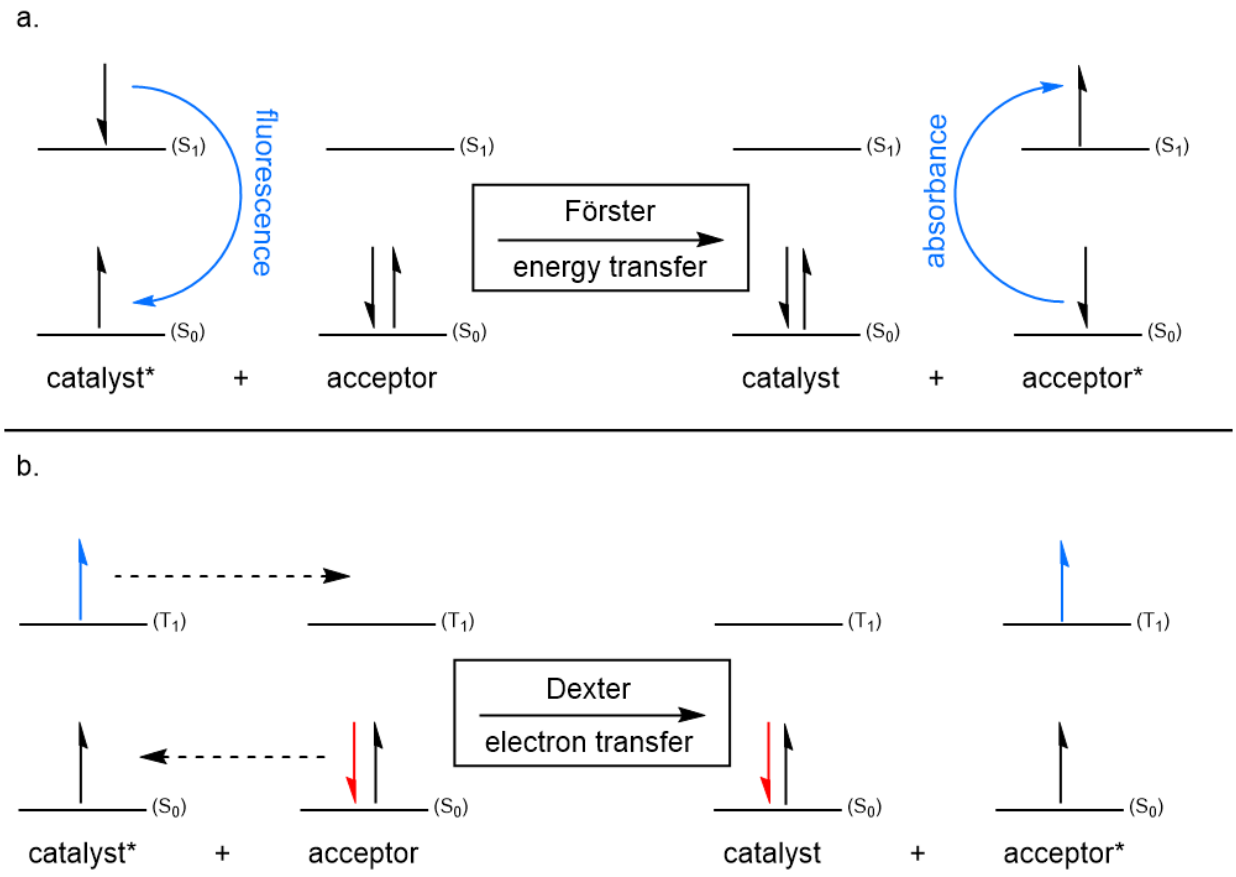

Figure 1.3 Two possible energy transfer mechanisms once the catalyst has been excited.

again, this process forms no polar intermediates, as both compounds are reduced and oxidized at the same time.[8]

If the excited state of the catalyst exchanges electrons in separate steps (creating charged intermediates), different redox reactivity can be achieved. This is important because the excited state of a sensitizer is a much more potent reductant and oxidant than when it is in the ground state. As shown in Figure 1.4 with the transition metal catalyst $Ru(bpy)_3^{+2}$, the catalyst in its ground state absorbs a photon and promotes an electron from the t_{2g} orbital of the metal center into the π^* orbital in the

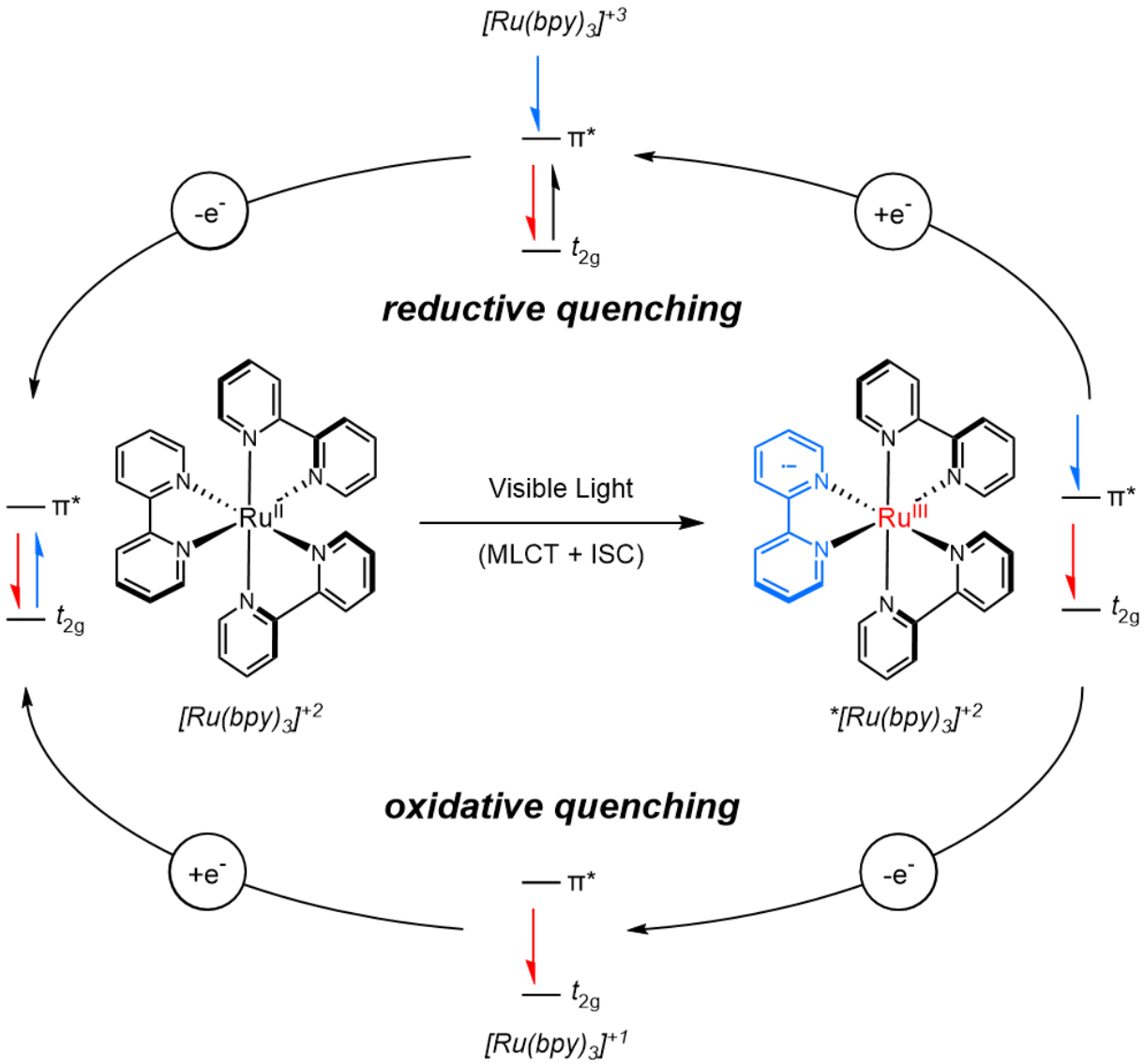

Figure 1.4 Possible quenching mechanisms for the transition metal photosensitizer, $[Ru(bpy)_3]^{+2}$.

bipyridine ligand. This electron transfer to the ligand from the metal center is called a metal to ligand charge transfer (MLCT) and effectively oxides the Ru(II) to Ru(III) while reducing the ligand surrounding it. As the excited electron begins to relax, it may undergo previously mentioned intersystem crossing to create the long lived (1100 ns) and reactive triplet state. In this state, the catalyst may accept an electron into its lowest SOMO in the presence of some reductant or donate an electron from its highest SOMO in the presence of an oxidant. Once either process occurs, a matched redox event most occur to return the catalyst to its ground state. [9]

To predict what pathway a catalyst and substrate may take, standard reduction potentials (SRPs) are used to predict reactivity. The more negative a SRP, the stronger the catalyst is as a reducing agent and the more positive the SRP, the stronger it is as an oxidizing agent. For $Ru(bpy)_3^{+2}$ in its excited state, it has a SRP of -0.81V vs. standard calomel electrode (SCE) following the oxidative quenching cycle, or a SRP of 0.77 V vs. SCE following the reductive quenching pathway. The matched redox events that terminates each route typically result in a stronger oxidant or reductant. For $Ru(bpy)_3^{+3}$, it has a SRP of 1.29 V vs. SCE, while $Ru(bpy)_3^{+1}$ has a SRP of -1.33 V vs. SCE. In this work, a particular focus will be given to how aryl and alkyl amines can be leveraged in photoredox systems as substrates (Chapter 2 and 3) in a redox neutral system or as a source of electrons (Chapter 4) in an overall reductive system. This is because amines are fairly easy to oxidize and typically only have a SRP of 0.7 V to 1.0 V vs. SCE making them ideal partners for reductive quenching mechanisms.[10]

The SRPs that a catalyst can reach can be tuned for both transition metal catalysts and metal free organic catalysts to achieve increasingly difficult reductions or oxidations. To this end, many groups have developed catalysts beyond the $Ru(bpy)_3^{+2}$ sensitizer. In this work, the use of an iridium based complex and metal-free cyanoarene were used to achieve the desired reactivity.[11,12]

1.4 Photoredox Catalysis for Synthesis

Photochemical reactions on a whole are typically recognized for their mild conditions (in comparison to thermal reactions). In fact, early consideration of "green" and "sustainable" synthesis was born at the same time as photochemistry.[6] Photoredox as a method can set itself apart further by its ability to generate powerful reductants and oxidants in catalytic quantities. This is due to the catalytic use of a sensitizer and the excited state lifetime being relatively short. This in turn allows radicals to be generated in a similar catalytic quantity, allowing for greater control over the bond formation desired. This is in stark contrast to radical generating methods that may involve elevated temperatures or hazardous radical imitators such as tin which generate many reactive intermediates.

Photoredox itself has seen a resurgent recently. Although early seminal work on synthetic applications of photoredox can be found in the later 1970s and early 80s[13-15], it was not until 2008 that the field received renewed attention thanks to the groups of Yoon, MacMillan, and Stepheson who independently published work that showed the ability of photoredox to tackle a large selection of synthetic problems. Yoon reported an impressive intramolecular [2+2] cycloaddition reaction involving two enones to form cyclobutane containing products.[16] Macmillan disclosed an asymmetric alkylation of aldehydes accomplished using both photoredox and enamine organocatalysis.[17] Stephenson tackled a tin-free reductive dehalogenation using the aforementioned $Ru(bpy)_3Cl_2$ sensitizer.[18] The use of amines and the alpha amino radical to form C-C bonds was not achieved until later in 2011-2012 by the groups of MacMillan, Nishibayashi, Pandey, and Resier.[19-21] Since these reports, the field of photoredox enable reactions has exploded. The following three chapters outline the small advances made in this field that rely on the most readily available source of energy: light.

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Chapter 2:

Synthesis of Unnatural Amino Acids and Peptides using Aminoalkyl Radicals

Figure 2.1 Authors Adam Aycock (left) and Cam Pratt (right) at SERMACS 2018 with the ACS mascot "Professor Molenium".

Reprinted and adapted with permission from (R. A. Aycock,‡ **C. J. Pratt**,‡ and N. T. Jui Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides. ACS Catal. 2018, 8, 9115-9119.)

‡**Both Authors contributed equally to this work.**

2.1 Introduction

As outlined previously, the generation of the alpha amino radical via photoredox conditions has already been well established in the field. From the pioneering work of Mariano and Pandey[22,23] to the numerous additional studies by MacMillan,[19] Reiser,[20] Nishibayashi,[21] Yoon,[24,25] and others[26-34] it is clear that α-amino radicals, accessed via visible-light photoredox catalysis[9,35] can be utilized in a diverse array of powerful synthetic transformations.

To access this radical intermediate, pre-functionalized amines (e.g., α-silylamines, amino acids, or aminoalkylboronates) allow for programmed radical formation, at the cost of additional steps to the desired amine structure. Whereas unfunctionalized amines (this work) may also serve as sources for these radical intermediates (at the cost of regioselectivity in some situations). Radical formation is either through direct hydrogen atom abstraction[36] or sequential single electron oxidation and C−H deprotonation.[37-40]

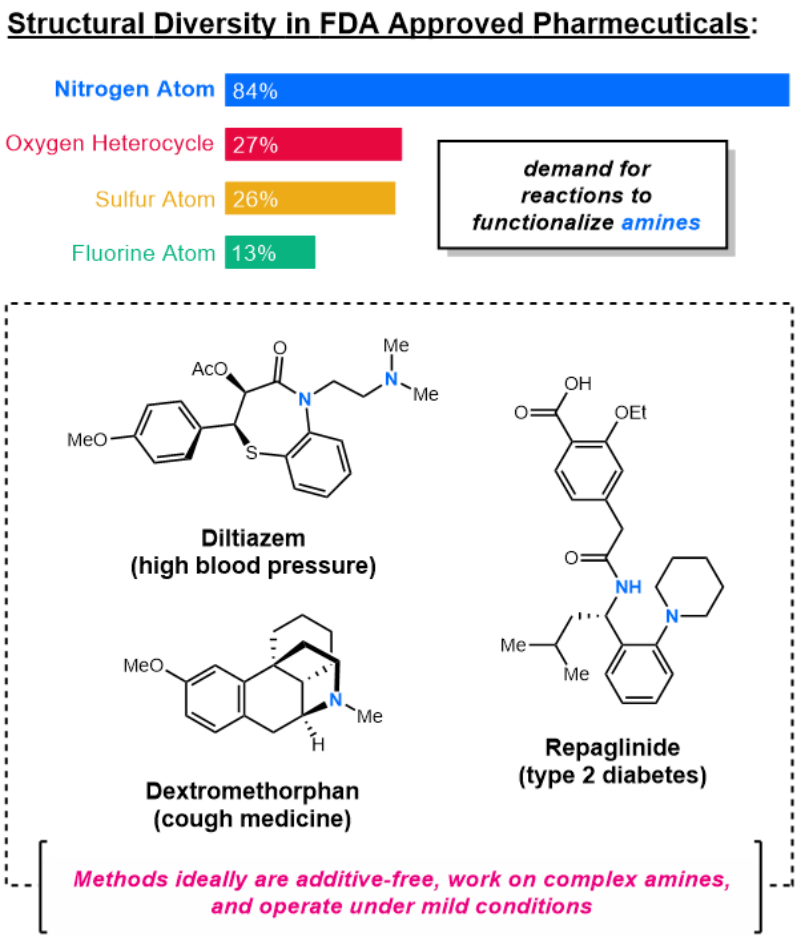


Figure 2.2 Most common heteroatoms found in everyday pharmaceuticals with examples provided.

This radical is of particular interest to us because it directly involves one of the most commonly found heteroatom in pharmaceuticals: the nitrogen atom (see Figure 2.2 for

details).[41] Rather than utilizing the typical disconnection of a nitrogen atom acting as a deprotonated anionic nucleophile to some electrophilic partner, the alpha amino radical displays nuclephilic behavior on the carbon next door to the nitrogen allowing for C-H functionalization. Generation of this intermediate using an oxidizing photosensitizer is of particular importance because it allows for highly complex amines to be activated in a chemoselective manner. Typically, good partners for these radicals are electron-poor olefins which undergo radical conjugate addition type reactions without the need for harsh conditions. Our goal was to apply this powerful intermediate to the generation of unnatural amino acids and peptides using dehydroalanine (Dha) as the most logical coupling partner.

Modification of peptides is already an important challenge for organic chemists and has undergone a great deal of study. Methods developed for amino acid containing systems typically require the use of aqueous media, thermally mild conditions, and must be tolerant to the presence of other nucleophilic species. To this end, many examples of biochemical strategies that harness enzymatic ligation systems[42] and specific incorporation of non-natural amino acids[43] has already been utilized successfully. These methods along with "click" reactions that can be performed in conditions similar to living cells[44,45] and play a central role in nonnatural protein and peptide synthesis. Furthermore, the natural reactivity of specific residues such as cysteine, lysine, or N-terminal amines has also been used to accomplish the necessary bioconjugation.[46-49] The most recent advances involve olefin metathesis[50,51] nucleophilic aromatic substitution (S_NAr)[52,53] and transition-metal mediated processes[54-57] and have yielded reactions that proceed even under the typically very complex environments with impressive efficiency and selectivity.

The application of radical intermediates to these systems may seem counter intuitive. Most organic textbooks show organic radicals as highly reactive intermediates that propagate reactions in an uncontrollable manner until terminated at some later stage. In reality, radicals similar to the alpha amino radical are perfectly suited for use in the polar and heteroatom-rich environment found in

peptide chemistry. The MacMillan lab has already shown how photoredox catalysis can perform selective activation of C-terminal carboxylates[58,59] which upon single electron oxidation decarboxylate furnishing a radical that can react with conjugate acceptors in macrocyclization processes and site-selective intermolecular ligations.

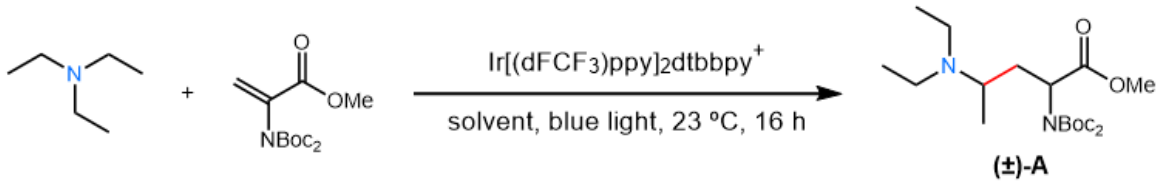
Specifically, the addition of radicals to Dha has also been shown by Davis[60] and Park[61] independently. In their work, primary alkyl radicals were formed from stoichiometric reduction of corresponding halides. These radicals would quickly undergo radical conjugate addition to dehydroalanine and provided more evidence for the possibility of simple backbone alteration via C−C bond formation (a similar feature of this work). It should be noted that the incorporation of Dha residues is also fairly well established, even in the protiens.[62]

Here, we show the development of reaction conditions that allow for an impressive range of unactivated and complex amines to be incorporated into amino acids with complete diastereocontrol. This is possible thanks to the use of the Karady−Beckwith chiral Dha substrate[63-65]. Thanks to the help of the co-author Adam Aycock, these conditions are also translated into a new system for peptide functionalization.

2.2 Results and Discussion

Triethylamine and dehydroalanine were used to evaluate the feasibility of this proposal. To effectively oxidize the amine, an iridium photocatalyst was found to work most efficiently (however other catalysts with excited state oxidations around 1.0 V worked as well, see section 2.4 for more details including an organic photocatalyst). Solvent flexibility was impressive, but acetonitrile and DMSO were largely used to mediate the desired conjugate addition. A key finding from this work involving amine loading is shown in Table 2.1. The amine loading is not important for conversion, but it is important for formation of the desired single-functionalized product. Under low amine loadings, many products containing the amine could be oxidized again creating new products that

Table 2.1 Reaction development made to look easy.



Entry	Solvent	Amine Equivalent	% yield A
1	**DMSO (0.1 M)**	3	72
2	**DMF (0.1 M)**	3	84
3	**DMA (0.1 M)**	3	87
4	**NMP (0.1 M)**	3	75
5	**H_2O (0.1 M)**	3	24
6	**MeCN (0.1 M)**	3	83
7	MeCN (0.1 M)	**1**	39
8	MeCN (0.1 M)	**2**	77
9	MeCN (0.1 M)	**3**	86
10	MeCN (0.1 M)	**5**	88
11	MeCN (0.1 M)	**10**	> 99

Key Finding: Amine loading must be in excess (to avoid product re-functionalization)

contained two Dhas groups. Typically, three to five equivalents of the starting amine were used to ensure the desired product was formed with excellent efficiency.

Translation from using the simple Dha to the chiral Dha substrate was gratifyingly smooth. A mechanistic blueprint for this reaction is illustrated in Figure 2.3. The oxidative α-amino radical formation is formed following one electron oxidation of the nitrogen followed by deprotonation of the alpha carbon's hydrogen. The desired C-C bond is formed via radical conjugate addition to the Dha substrate. After a single electron reduction of the resulting radical species (closing the catalytic cycle), protonation of the corresponding enolate delivers the desired product.

Inspired by a report by Molander,[66] an additive survey was also used to rapidly assess the expected chemoselectivity of this process. The outlined catalytic amine conjugation system was

tolerant of indole, phenol, sodium propionate, and imidazole, (as models for tryptophan, tyrosine, carboxylates, and histidine, respectively. Butyl mercaptan (a cysteine model) was also used, although thiol conjugate addition was competitive in this case.

The scope of the amine substrate was investigated next. As shown in Table 2.2, a wide range of aniline derivatives with varied electronic properties were able to undergo activation and conjugate addition, giving the corresponding unnatural amino acid derivatives with complete selectivity for the *cis*-isomer as suspected from previous findings.[65] It should be noted that acid deprotection of the chiral Dha is possible and provided the product in 96% ee for the major enantiomer (*N*,*N*-Dimethylaniline was used as the amine for this case). Electron-withdrawing aniline substrates are especially impressive

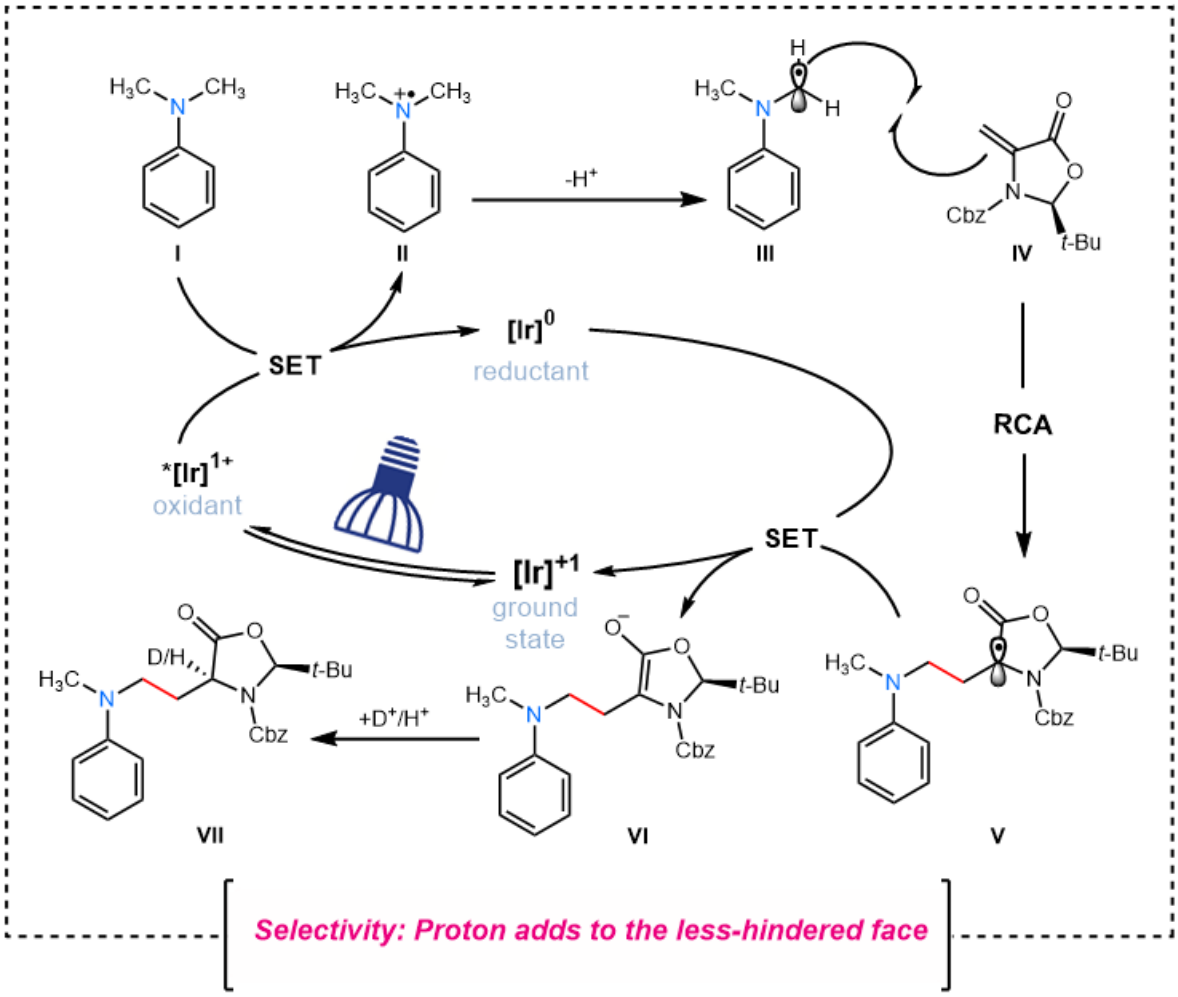
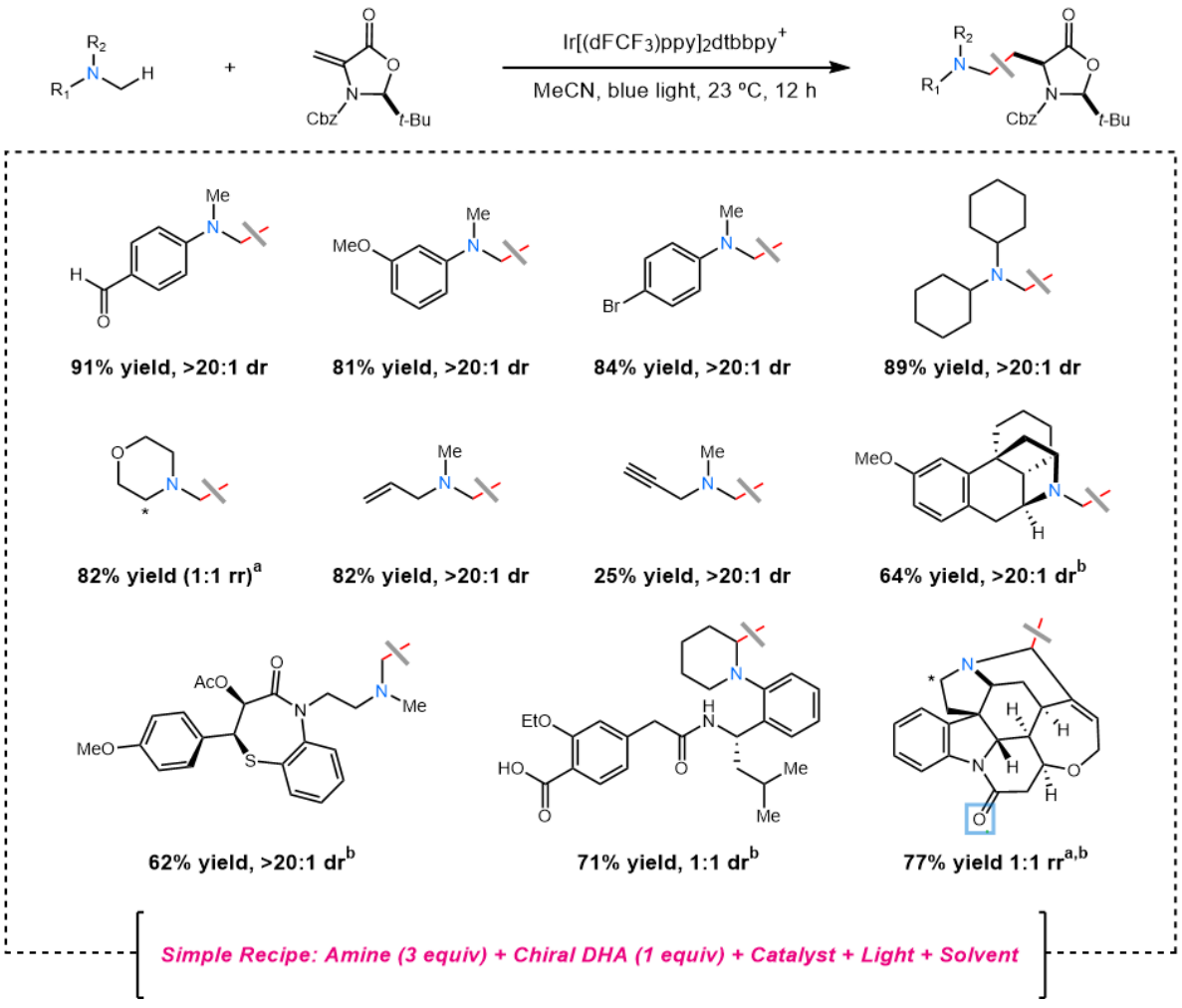


Figure 2.3 Proposed mechanistic pathway for direct conjugate addition of unactivated amines to dehydrolanines.

under these conditions. As highlighted first, the benzaldehyde function (which is a biorthogonal coupling unit), was passed through into the final product in an impressive 91% yield. The 3-methoxy-substituted aniline gave an 81% yield. However, this electron donating group in the ortho- or para-position of the aryl unit was unreactive, which is analogous to previous findings.[24] The aryl bromide was preserved under these conditions as well giving rise to an 84% yield. This shows how this method can translate other handles down a synthetic route. Use of an aryl amine is effective for removing one location of possible of radical formation. However, the arylamine is not required for the desired coupling with Dha. Specifically, methyldicyclohexylamine reacted in a similarly high yield of 89% to

Table 2.2 Amine C−H Activation/Conjugate Addition to Chiral Dehydroalanine (Dha): Tertiary Amine Scope. [a]Combined yield of two regioisomers, asterisk shows alternate connectivity. [b]Solvent changed to DMSO and amine loaded at 5 equiv.



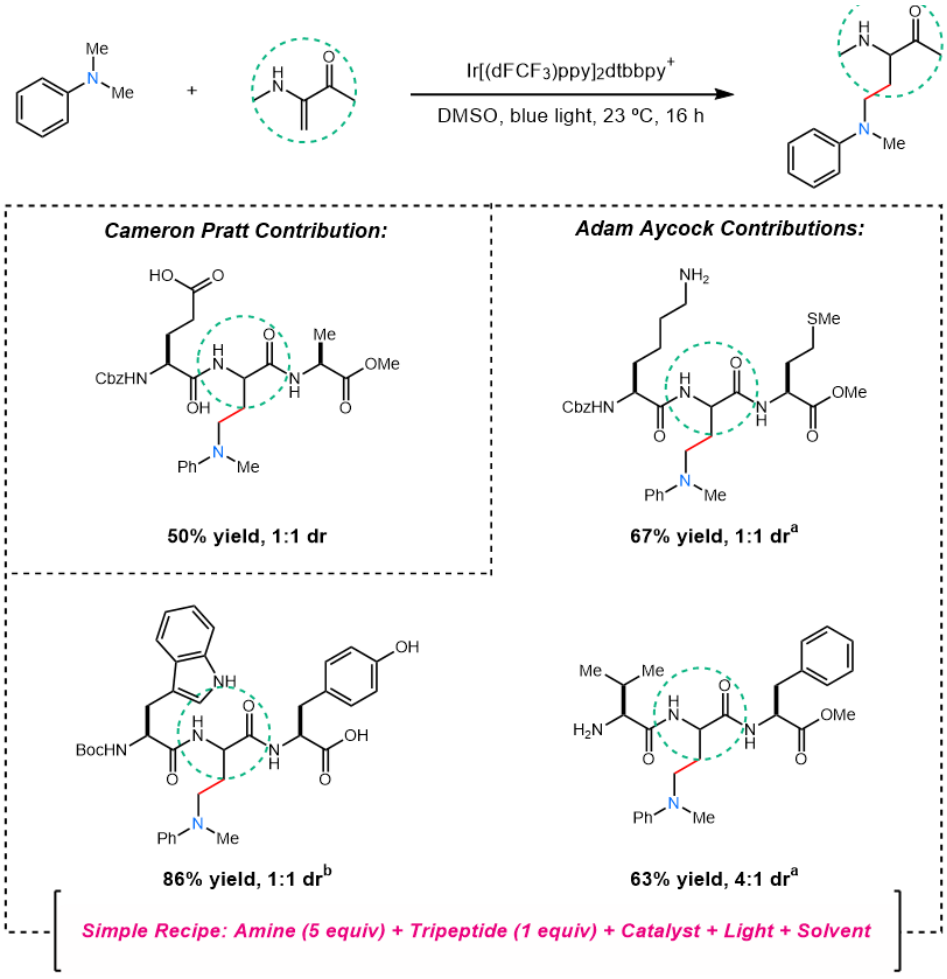
give the methyl functionalized product exclusively. However, the use of *N*-methylmorpholine gave rise to three isomeric products. In this case, both methyl and endocyclic methylene activation were observed. We observed selective formation of allylic and propargylic amines (in 82% and 25% yield, respectively), sadly the conversion of the clickable alkyne substrate was noticeably low.

To show this method working on complex amines, we applied this method to the direct functionalization of multiple bioactive tertiary amines available commercially. Activation of the *N*-methyl groups in the morphinan dextromethorphan (check your medicine cabinet for this compound in common cold medicines) and calcium channel blocker diltiazem occurred under slightly altered standard conditions (DMSO used as solvent, amine loading increased to 5 equiv), giving rise to acceptable yields (64% and 62%, respectively). Regioselective reaction of the *N*-arylpiperidine repaglinide gave two diastereomers in equal amounts (71% combined yield). Finally, the complex alkaloid and rodent poison strychnine was applied to this system. In this case, we expected multiple regioisomeric products to form. Two major products were isolated from this reaction in equal amounts. By using the COSY spectrum from the new products and comparing them to the un-functionalized strychnine we were able to assign each product. This was largely possible thanks to the two isolated spin systems present in strychnine that contain the methylene carbons alpha to the oxidizable nitrogen. The product shown in table 2.2 contained the uninterrupted CH_2-CH_2 spin system, while a clear absence of the spin system isolated by the substituted alkene was found. In the other product (indicated by the asterisk), the opposite is observed. Here the CH_2-CH_2 spin system is interrupted, while the simple methylene carbon's spin system isolated by the totally substituted alkene is clearly present.

After showing how complex amines could be applied to the relatively simple chiral Dha, we next investigated Dhas in simple tri-peptides. The goal was to continue to probe the tolerance of the process to potentially reactive residues. As seen in Table 2.3, the amine dimethylaniline was applied to

a range of tripeptides. This author contributed to the work of the unprotected side-chain carboxylate containing peptide which under the reaction conditions delivered a functionalized Cbz-Glu-Dha-Ala-OMe product in 50% yield (1:1 dr observed, due to lack of preferred face of protonation). Adam Aycock made the other tripeptides and found similarly impressive results. Specifically, the desired alkylamine conjugate addition was not impacted by the indole, phenol, or terminal carboxylate in Boc-Trp-Dha-Tyr-OH and gave the product in 86% yield. The free amine containing Cbz-Lys-Dha-Met-OMe peptide could proceed under slightly acidic conditions and gave its product in 67% yield. Finally, reaction of H_2N-Val-DhaPhe-OMe (again, as the trifluoroacetic acid salt) afforded the desired product without being affected by unprotected N-terminal amine at a 63% yield. This product showed some

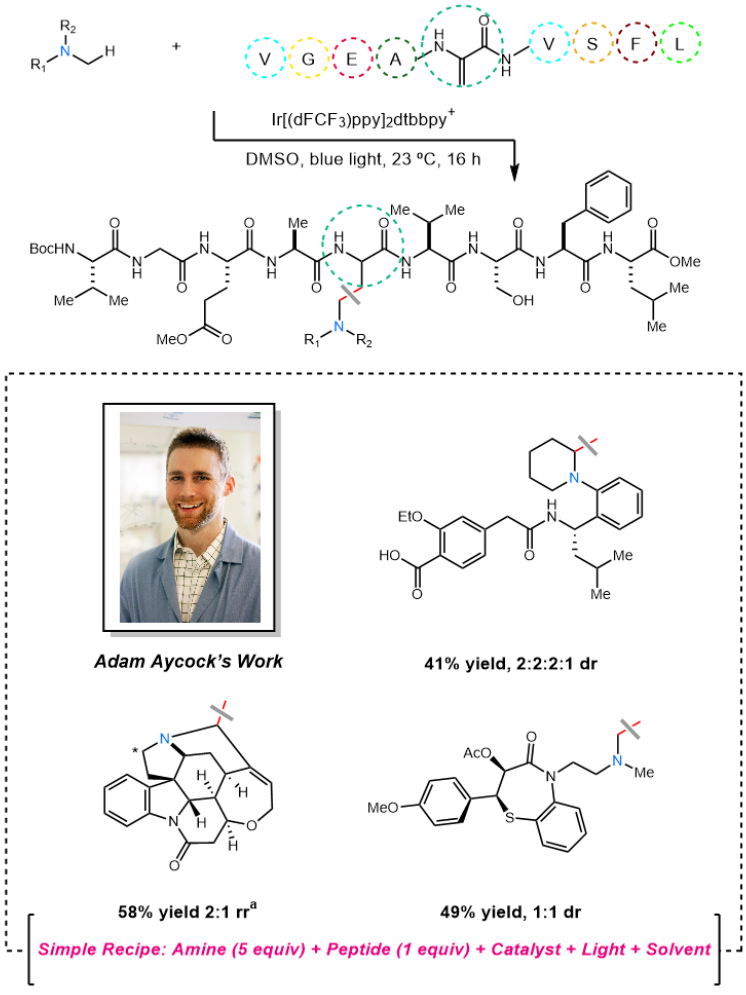
Table 2.3 Addition of dimethylaniline to Dha tripeptides. [a]Reactions ran with peptide trifluoroacetic acid salt. [b]Catalyst changed to Ir(ppy)$_2$dtbbpy·PF6 at 1% loading



slightly higher diastereoselectivity likely due to the bulky isopropyl group present near the site of protonation.

Finally, Adam Aycock showed how a complex peptide shown in Table 2.4 could also handle the incorporation of complex amines shown previously by the author. A slight change in conditions to DMSO and an increase amine loading to 5 equivalents was utilized to ensure the large peptide would dissolve and the amine would be functionalized only once. This peptide was prepared using standard solution-phase peptide-coupling procedures and subsequent elimination of the internal cysteine thiol to provide the necessary Dha handle. Effective conjugate addition of amine substrates was observed by HPLC. Regiochemical assignments (or amine activation sites) were made in analogy to RCA adducts from Table 2.2, and yields refer to isolated yields of diastereomeric mixtures that were obtained by preparative HPLC. Repaglinide could be directly appended to this peptide backbone with good efficiency providing a 49% yield and a 1:1 dr. Diltiazem performed slightly worse giving a 41% yield and 2:2:2:1 dr. The strychnine peptide conjugate was furnished as an inseparable mixture of regioisomers and diastereomers in the highest yield at 58%. Once again, C−C bond formation

Table 2.4 Addition of dimethylaniline to Dha peptide. [a]Combined yield of two regioisomers, asterisk shows alternate connectivity



occurred at both of the α-amino methylene positions within this natural product. Once again, this method proved how exclusive activation of the desired aniline (or amine) could be obtained even in the presence of a range of acidic or otherwise challenging groups.

2.3 Conclusion

This project showcases how the alpha amino radical formed from a wide range of tertiary amines can be applied to peptide systems that contain the key partner dehydroalanine. This system is driven by light and is highly chemoselective. Thanks to the photoredox driven mechanism, the method operates at room temperature and requires no additional additives (beyond the photosensitizer loaded in at 1 mol %). A key finding from this work that is present in the rest of the chapters is how amine loading affects the product distribution. By increasing amine loading, it is possible to out compete product functionalization (however if this is desired it is also possible to obtain by lowering amine loading). Because the method was also found to be highly tolerant of a range of solvents, we were able to show that this reactivity can be applied to the synthesis of highly complex unnatural amino acids and peptides with good efficiency.

2.4 Supporting Information

2.4.1 General Information

All reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (PARsource PowerPAR LED Bulb-Blue 15 Watt/440 nm, available at www.1000bulbs.com). Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photoredox catalysts, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and $[Ir(ppy)_2(dtbbpy)]PF_6$ were prepared according to literature procedures.[11,67] Anilines, amino acids, HBTU, DIPEA, Ellman's reagent, methanesulfonyl chloride, triethylsilane, DBU, piperidine, TFA, and tertiary amines were purchased from Aldrich Chemical Co., Alfa Aesar, Combi Blocks, or

Oakwood Products and were used as received. Boc-Trp-Dha-Tyr-OH used to prepare **19** was prepared according to literature procedure.[68] Methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate and benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate was prepared according to literature procedure.[65,69] DMSO and MeCN were purified on a Pure Process Technologies solvent purification system. Reaction solvents were degassed in a sidearm flask under weak vacuum while subject to sonication.

All yields refer to isolated yields. New compounds were characterized by NMR, IR spectroscopy, and HRMS. NMR data were recorded on one of four spectrometers: Bruker 600 MHz, INOVA 600 MHz, INOVA 500 MHz, and INOVA 400 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR; $(CD_3)_2CO$: 2.05 ppm for ^{1}H NMR and 29.84, 206.26 ppm for ^{13}C NMR; CD_3OD: δ 3.31 ppm for ^{1}H NMR and 49.1 ppm for ^{13}C NMR, or D_2O). IR spectra were obtained with a Thermo Scientific Nicolet iS10 Fourier transform infrared spectrophotometer. Mass spectrometry data were obtained from the Emory Mass Spectrometry Center. Adduct yields for optimization and deviation data was obtained via ^{1}H NMR with an INOVA 600 MHz NMR using 1,3-benzodioxole as the internal standard. Enantioenriched samples were analyzed on a Varian Prostar instrument and used isopropanol/hexane as gradient.

2.4.2 General Procedures

Radical Conjugate Addition Procedure with MeCN as Solvent: A screw-top test tube equipped with a stir bar was charged with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%), benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (1 equiv), and amine or aniline if solid (3-5 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with degassed solvent (MeCN, 10 mL/mmol

benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate) and amine or aniline if liquid (3-5 equiv) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 12-16 hours. The reaction mixture was passed through a plug of silica which was flushed with ethyl acetate, and the solution was transferred to a 20-mL scintillation vial. The contents of the vial were concentrated via rotary evaporation and then subject to high vacuum for 2 hours. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

Radical Conjugate Addition Procedure with DMSO as Solvent: A screw-top test tube equipped with a stir bar was charged with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%), benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (1 equiv), and amine or aniline if solid (3-5 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with degassed solvent (DMSO, 10 mL/mmol benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate) and amine or aniline if liquid (3-5 equiv) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 12-16 hours. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (5 x 5 mL). The extracts were combined and passed through a plug of silica which was flushed with additional ethyl acetate, and the solution was transferred to a 20-mL scintillation vial. The contents of the vial were concentrated via rotary evaporation and then subject to high vacuum for 2 hours. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

Procedure for Removal of Tertbutyl Carbamate: The N-Boc protected peptide was treated with neat trifluoracetic acid (10 equiv) and allowed to stir for 10 minutes. Reaction progress was monitored by LCMS, and upon completion, the mixture was concentrated directly and excess solvent

was azeotropically removed with chloroform three times. The product was taken forward without further purification.

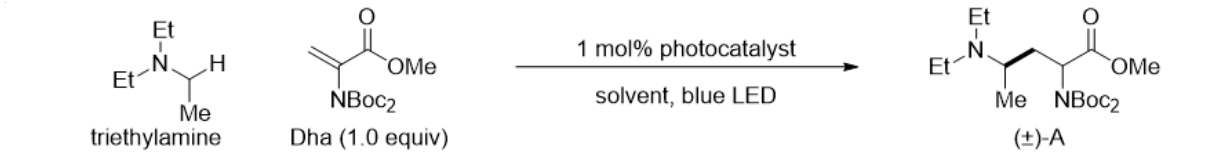
Peptide-Coupling Procedure: A round-bottom flask equipped with magnetic stir bar was charged with N-protected free carboxylic acid (1.0 equiv) and DMF (0.5 M) and was cooled to 0 ºC. HBTU (1.0 equiv) was added in a single portion, followed by DIPEA (3.5 equiv). The amine coupling partner was dissolved in DMF (10 mL) and added to the reaction mixture dropwise. After stirring 10 minutes, the reaction mixture was allowed to warm to room temperature. Reaction progress was monitored by LCMS, and complete conversion was typically observed within two hours. The reaction mixture was partitioned between a saturated aqueous solution of NH_4Cl and ethyl acetate. The organic layer was washed with NH_4Cl (3x), $NaHCO_3$ (2x), and brine (1x). The organic layer was passed through a short pad of silica and concentrated by rotary evaporation. The resultant white solid was taken forward without further purification.

Radical Conjugate Addition Procedure with Dha Peptide: A screw-top test tube equipped with a stir bar was charged with Dha peptide(1 equiv), and amine or aniline if solid (5 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with a stock solution of degassed solvent with catalyst (DMSO, 1.0 mL/mmol Dha peptide, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, (0.1 mg/mL) and amine or aniline if liquid (5 equiv) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 12-16 hours. A 100 μL aliquot was diluted with methanol (400 μL) and subjected to LCMS analysis. The LCMS sample was recombined with the reaction mixture and purified directly by preparative HPLC and lyophilized to afford the title compound.

2.4.3 Optimization Details

A screw-top test tube equipped with a stir bar was charged with photoredox catalyst (1-5 mol%) and methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (60 mg, 0.2 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with degassed solvent (2.0 mL) and triethylamine (84 µl, 0.6 mmol, 3 equiv) by syringe. The resulting solution was stirred under irradiation with blue LEDs for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (5 x 5 mL). The extracts were combined and passed through a plug of silica which was flushed with additional ethyl acetate, and the solution was transferred to a 20-mL

Table S2.1 The influence of solvent, catalyst, and amine equivalents on yield of triethylamine mono-adduct (±)-A.



entry	photocatalyst	solvent	amine equivalent	% yield A
1	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMSO (0.1 M)	3	72 (77:23 dr)
2	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMF (0.1 M)	3	84 (" dr)
3	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA (0.1 M)	3	87 (" dr)
4	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	NMP (0.1 M)	3	75 (" dr)
5	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	H_2O (0.1 M)	3	24 (" dr)
6	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN (0.1 M)	3	83 (" dr)
7	eosin Y[a]	MeCN (0.1 M)	3	12 (" dr)
8	$Ir(ppy)_2(dtbpy)(PF_6)$	MeCN (0.1 M)	3	81 (" dr)
9	$Ru(bpy)_3(PF_6)$	MeCN (0.1 M)	3	23 (" dr)
10	PDI[a]	MeCN (0.1 M)	3	10 (" dr)
11	PTH[a]	MeCN (0.1 M)	3	3 (" dr)
12	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN (0.1 M)	1	39 (" dr)
13	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN (0.1 M)	2	77 (" dr)
14	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN (0.1 M)	3	86 (" dr)
15	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN (0.1 M)	5	88 (" dr)
16	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN (0.1 M)	10	> 99 (" dr)

[a]5 mol% photocatalyst

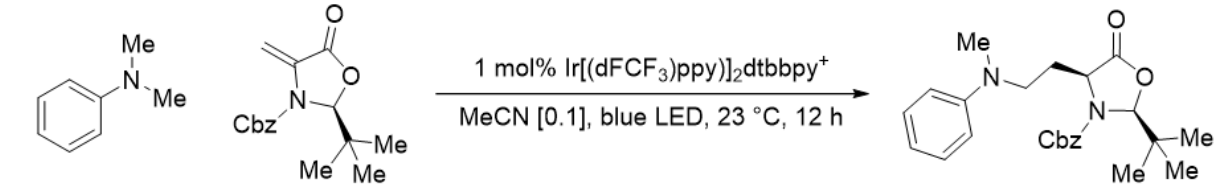
scintillation vial. The contents of the vial were concentrated via rotary evaporation. An internal standard of 1,3-benzodioxole (23 μL, 1 equiv) was delivered to the vial, and the contents were thoroughly dissolved in $CDCl_3$. An aliquot was analyzed by ^1H NMR and the integral values were used to calculate yield.

Deviation Procedure when MeCN is used as Solvent: A screw-top test tube equipped with a stir bar was charged with photoredox catalyst (1 mol%), methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (60 mg, 0.2 mmol, 1 equiv), and solid deviation as indicated (0.2 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with degassed MeCN (2.0 mL), *N,N*-dimethylaniline (76 μl, 0.6 mmol, 3 equiv), and liquid deviation as indicated (0.2 mmol, 1 equiv) by syringe. The resulting solution was stirred under irradiation with blue LEDs for 12 hours. After 12 hours, the reaction mixture was transferred to a 20-mL scintillation vial. The contents of the vial were concentrated via rotary evaporation. An internal standard of 1,3-benzodioxole (23 μL, 1 equiv) was delivered to the vial, and the contents were thoroughly dissolved in $CDCl_3$. An aliquot was analyzed by ^1H NMR and the integral values were used to calculate yield.

Deviation Procedure when DMSO is used as Solvent: A screw-top test tube equipped with a stir bar was charged with photoredox catalyst (1 mol%) and methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (60 mg, 0.2 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with degassed DMSO (2.0-1.0 mL), *N,N*-dimethylaniline (76 μl, 0.6 mmol, 3 equiv), and water as indicated by syringe. The resulting solution was stirred under irradiation with blue LEDs for 12 hours. After 12 hours, the reaction mixture was quenched with

saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (5 x 5 mL). The extracts were concentrated via rotary evaporation into a 20 ml scintillation vial. An internal standard of 1,3-benzodioxole (23 μL, 1 equiv) was delivered to the vial, and the contents were thoroughly

Table S2.2 Results of yield of amine-Dha conjugate addition product caused by deviations to developed conditions.



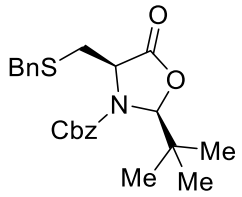
N,N-dimethylaniline chiral Dha amine-Dha conjugate addition

entry	deviation from optimal conditions[a]	chiral Dha remaining	yield[b]
1	none	0%	81%
2	without light	100%	0%
3	without catalyst	100%	0%
4	1 eqv. indole	0%	92%
5	1 eqv. phenol	60%	28%
6	1 eqv. sodium propionate	0%	81%
7	1 eqv. imidazole	0%	87%
8	1 eqv. butyl mercaptan	0%	31%[c]
9	1 eqv. acetic acid	0%	73%
10	1 eqv. sodium acetate	0%	75%
11	1 eqv. pyridine	0%	87%
12	1 eqv. ethanol	0%	93%
13	DMSO as solvent	0%	81%
14	DMSO : H_2O (9 : 1) as solvent	24%	75%
15	DMSO : H_2O (3 : 1) as solvent	67%	33%
16	DMSO : H_2O (1 : 1) as solvent	76%	12%
17	eosin Y as catalyst	53%	26%
18	neat (20 eqv. *N,N*-dimethylaniline)	0%	99%
19	MeCN [1.0]	0%	81%
20	MeCN [0.01]	0%	80%
21	MeCN [0.001]	0%	71%

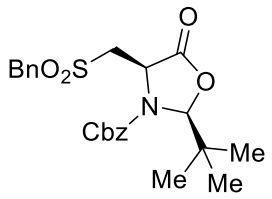
[a]conditions : *N,N*-dimethylaniline (0.6 mmol), chiral Dha (0.2 mmol), Ir[(dFCF$_3$)ppy)]$_2$dtbbpy-PF_6 (1 mol%), MeCN (2 mL), blue LED, 23 °C, 12 h. [b]yield determined by NMR. [c]70% yield of competitive thiol conjugate addition observed.

dissolved in $CDCl_3$. An aliquot was analyzed by ^1H NMR and the integral values were used to calculate yield.

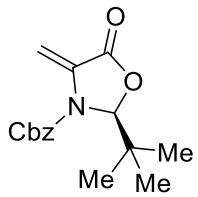
2.4.4 Preparation of Starting Materials



S-7benzyl (2S,4R)-4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate: To a round bottom flask equipped with a stir bar was added S-benzyl-L-cysteine (10 g, 47 mmol, 1 equiv.), NaOH (1.8 g, 45 mmol, 0.95 equiv), and anhydrous MeOH (500 mL). The reaction was stirred at room temperature for 30 minutes. Trimethylacetaldehyde (6.18 ml, 57 mmol, 1.2 equiv) and activated 3 Å molecular sieves (50g) were added to the reaction flask, each in one portion. The reaction was placed under nitrogen atmosphere and stirred at room temperature until the starting material had been consumed (determined by ^1H NMR of a filtered and concentrated aliquot of the reaction solution dissolved in D_3COD). The reaction was quickly filtered through celite and concentrated by rotary evaporation. The residue was dried under high vacuum for 24 hours to afford the imine as a white solid. The imine was dissolved in anhydrous DCM (500 mL) and cooled to -30 °C. Benzyl chloroformate (10.1 mL, 71 mmol, 1.5 equiv) was added to the reaction dropwise via syringe. The reaction was allowed to reach 0 °C. The reaction was stirred for a full 18 hours then warmed to room temperature and stirred for an additional 6 hours. The mixture was washed with 1 M aqueous NaOH (1x 250 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (0%–10% ethyl acetate/hexanes) to afford the product (8.3 g, 41% yield) as a colorless oil. The physical properties and spectral data were consistent with the reported values.[5] The racemate was synthesized from the racemic amino acid using the same procedure.

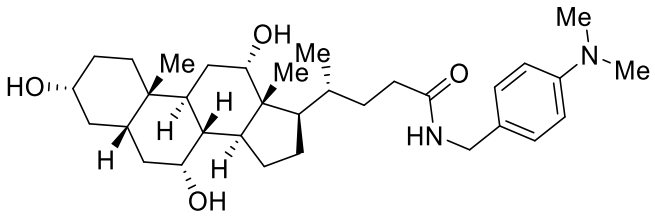


benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxy-late: To a round bottom flask equipped with a stir bar was added benzyl (2S,4R)-4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (6.3 g, 15.25 mmol, 1 equiv), *meta*-chloroperoxybenzoic acid (6.6 g, 38.12 mmol, 2.5 equiv), and DCM (205 mL). The reaction was stirred at room temperature for 18 hours. The reaction mixture was washed with 1 M aqueous sodium hydroxide (3 x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (10%–30% ethyl acetate/hexanes) to afford the product (5.5 g, 81% yield) as a white foam. The physical properties and spectral data were consistent with the reported values.[5] The racemate was synthesized from the racemic amino acid using the same procedure.



benzyl (S)-2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate(22): To a round bottom flask equipped with a stir bar was added (benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate) (5.5g, 12.4 mmol, 1 equiv), and DCM (155 mL).The flask was chilled to 0 °C in an ice bath, and DBU (2.1 mL, 13.6 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred at 0 °C until the starting material had been consumed (determined by TLC, about 10 minutes). While still at 0 °C, the reaction mixture was quenched with saturated aqueous ammonium

chloride (50 mL), the layers were separated, and the organic phase was washed with saturated aqueous ammonium chloride (3x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5%–10% ethyl acetate/ hexanes) to afford the product (3.4 g, 98% yield) as a white solid. The physical properties and spectral data are consistent with the reported values.[5] Chiral HPLC analysis of the alkene (OJ-H, 5% IPA/hexanes, 1.0 mL/min, 254 nm) indicated 99% ee for the major enantiomer (tR(minor) = 11.560 min, tR(major) = 13.130 min). The racemate was synthesized from the racemic amino acid using the same procedure.



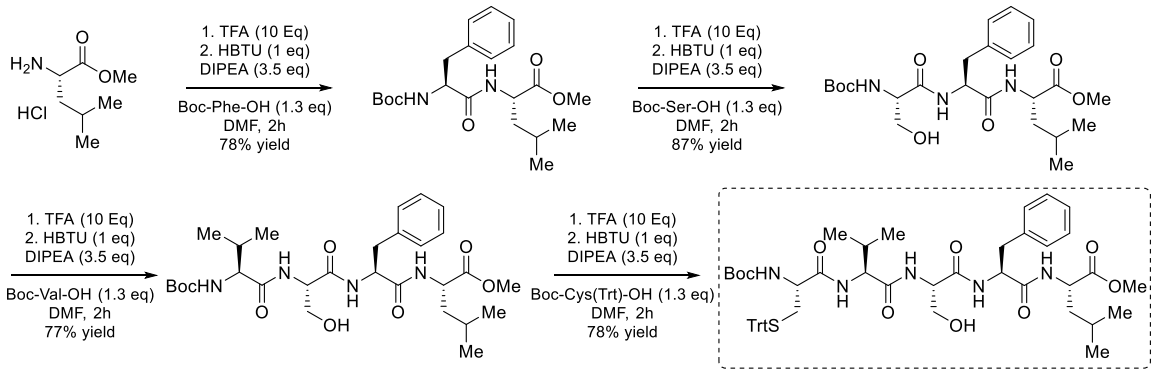
Aniline-tethered cholic acid: following the general procedure D, the reaction of cholic acid (250.1 mg, 0.61 mmol, 1.3 equiv), 4-dimethylaminobenzylamine (82 mg, 0.55 mmol, 1.0 equiv), HBTU (232 mg, 0.61 mmol, 1.0 equiv), and DIPEA (0.34 mL, 2.1 mmol, 3.5 equiv) provided the product (268 mg, 90% yield) as a yellow solid after purification by flash column chromatography 0-10% DCM/Methanol.

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.12 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 4.29 – 4.13 (m, 2H), 3.92 (d, J = 3.1 Hz, 1H), 3.78 (q, J = 3.0 Hz, 1H), 3.36 (tt, J = 11.2, 4.3 Hz, 1H), 2.88 (s, 6H) 2.32 – 2.19 (m, 3H), 2.18 – 2.08 (m, 1H), 2.01 – 1.91 (m, 2H), 1.90 – 1.76 (m, 4H), 1.76 – 1.68 (m, 1H), 1.65 (dp, J = 13.1, 3.7, 2.9 Hz, 1H), 1.61 – 1.48 (m, 5H), 1.46 – 1.19 (m, 6H), 1.08 (qd, J = 11.9, 5.6 Hz, 1H), 1.00 (d, J = 6.4 Hz, 3H), 0.91 (s, 3H), 0.66 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 175.01, 150.15, 128.27, 127.02, 112.88, 72.64, 71.48, 67.64, 46.70, 46.10, 42.45, 42.32, 41.80, 41.58, 39.78, 39.63, 39.07, 35.36, 35.10, 34.51, 34.48, 32.87, 32.81, 32.02, 29.79, 28.17, 27.28, 26.47, 22.86, 21.77, 16.33, 11.67.

FTIR (neat) ν_{max}: 2962, 2940, 2909, 2873, 1788, 1717, 1599, 1573, 1506, 1481, 1467, 1455, 1391, 1369, 1336, 1295, 1228, 1198, 1188, 1114, 1067, 1040, 1012, 991, 971, 943, 931, 910, 891, 866, 842, 824, 803, 785, 747, 733, and 693 cm^{-1}.

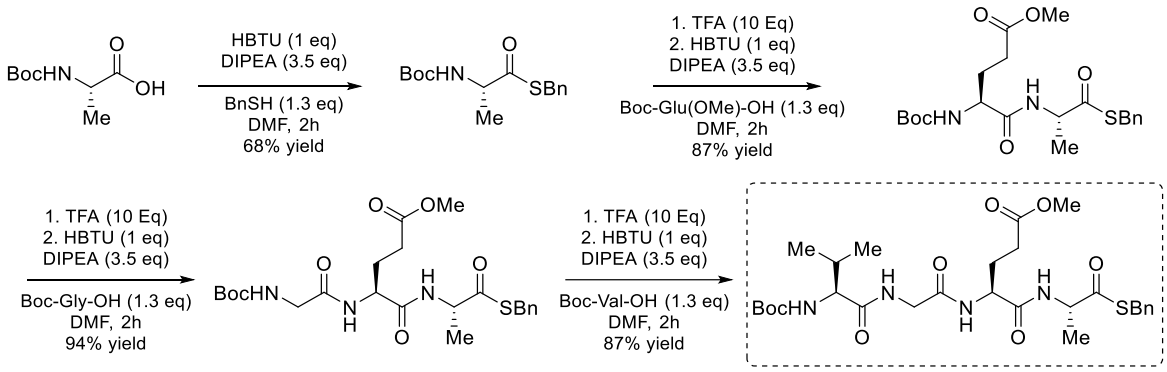
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{33}H_{53}O_4N_2$, 541.4000; found, 541.4002.



Scheme S2.1. Boc-Cys(Trt)-Val-Ser-Phe-Leu-OMe: prepared by sequential peptide coupling and deprotection steps (beginning from the H_3N-Leu-OMe • HCl) following general procedure D. The series of reactions provided the product as a white crystalline solid (5.1g) after passing through a short pad of silica (100 % ethyl acetate).

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.28 (d, J = 7.7 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.37 – 7.27 (m, 13H), 7.27 – 7.15 (m, 9H), 5.00 (s, 1H), 4.54 (td, J = 8.5, 4.7 Hz, 1H), 4.34 – 4.24 (m, 2H), 4.22 (dd, J = 9.0, 5.7 Hz, 1H), 3.80 (td, J = 8.6, 5.1 Hz, 1H), 3.61 (s, 3H), 3.53 – 3.42 (m, 2H), 3.06 (dd, J = 14.1, 4.7 Hz, 1H), 2.80 (dd, J = 14.1, 8.8 Hz, 1H), 2.41 (dd, J = 12.1, 9.0 Hz, 1H), 2.34 (dd, J = 12.2, 5.3 Hz, 1H), 1.93 – 1.80 (m, 1H), 1.64 – 1.45 (m, 3H), 1.38 (s, 9H), 0.86 (dd, J = 32.4, 6.5 Hz, 6H), 0.69 (dd, J = 27.7, 6.8 Hz, 6H).

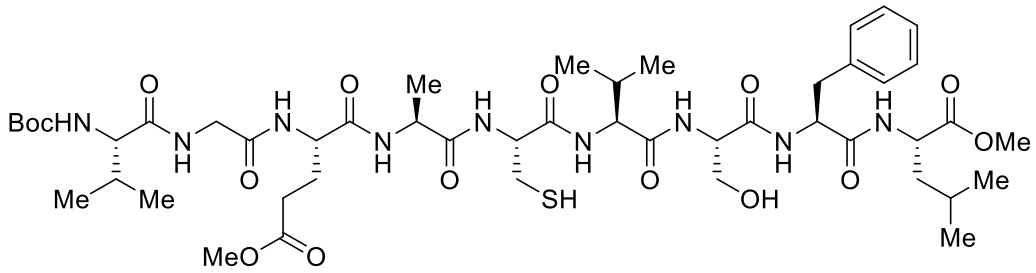
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{51}H_{65}O_9N_5NaS$, 946.4395; found, 946.4389.



Scheme S2.2. Boc-Val-Gly-Glu(OMe)-Ala-SBn**:** prepared by sequential peptide coupling and deprotection steps (beginning from Boc-Ala-OH) following general procedure D. The series of reactions provided the product as a white crystalline solid (4.1 g) after passing through a short pad of silica (100 % ethyl acetate).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.84 (m, 3H), 7.29 – 7.15 (m, 5H), 5.84 (d, J = 9.1 Hz, 1H), 4.86 (q, J = 7.1 Hz, 1H), 4.74 (t, J = 7.4 Hz, 1H), 4.32 (dd, J = 17.2, 6.1 Hz, 1H), 4.25 (t, J = 7.9 Hz, 1H), 4.07 (d, J = 3.3 Hz, 2H), 3.93 – 3.79 (m, 1H), 3.59 (s, 3H), 2.53 – 2.35 (m, 2H), 2.17 (dt, J = 14.4, 7.2 Hz, 1H), 2.02 (dt, J = 14.5, 7.3 Hz, 2H), 1.37 (s, 12H), 0.91 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{42}O_8N_4Na$, 617.2621; found, 617.2616.



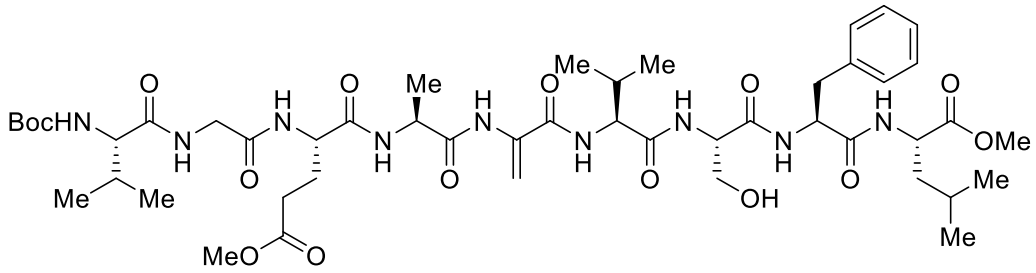
Boc-Val-Gly-Glu(OMe)-Ala-Cys-Val-Ser-Phe-Leu-OMe:

Boc-Cys(Trt)-Val-Ser-Phe-Leu-OMe (325 mg, 0.35 mmol, 1.3 equiv) was treated with TFA (5 mL), forming a dark yellow solution, and mixture allowed to stir 5 minutes until all solids were dissolved. To the stirring solution was added triethylsilane (0.1 mL) dropwise. All color faded from the mixture, and a white precipitate was observed. The mixture was concentrated by rotary evaporation and azeotropically removed with chloroform (3 x 10 mL). The resultant solids were dissolved in rigorously degassed DMF (5 mL), transferred to a screw-top test tube equipped with stir bar, capped with PTFE/silicon septum, connected to a Schlenk line under N_2, and extracted with hexanes (3 x 5 mL) via syringe. The hexanes layers were discarded. Boc-Val-Gly-Glu(OMe)-Ala-SBn (160 mg, 0.227 mmol, 1.0 equiv) was dissolved in degassed DMF, combined with the extracted DMF layer, and the mixture was allowed to stir (5 min). To the stirring solution was added triethylamine (0.5 mL), thiophenol (0.05 mL), and benzyl mercaptan (0.05 mL). The mixture was heated to 40 °C and allowed to stir 12 hours, after which a white precipitate had begun to form. 1 M HCl (35 mL) was added to the reaction mixture to fully precipitate the desired peptide, and the white solid was collected by vacuum filtration. The solid was rinsed thoroughly with 1M HCl, hexanes, and water. Finally, the solid was finely ground and triturated by stirring in MeCN at 70 °C for 30 minutes, before returning to room temperature. The suspension was filtered once more, and the solid was collected, yielding the title compound as a white solid (180 mg, 64% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.27 (d, J = 7.7 Hz, 1H), 8.17 (d, J = 7.1 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.07 (t, J = 5.7 Hz, 1H), 7.95 (dd, J = 12.9, 8.0 Hz, 3H), 7.72 (d, J = 8.6 Hz, 1H), 7.25 – 7.16 (m, 5H), 6.71 (d, J = 8.7 Hz, 1H), 4.99 (s, 1H), 4.55 (td, J = 8.6, 4.7 Hz, 1H), 4.43 (td, J = 7.8, 5.3 Hz, 1H), 4.29 (dddd, J = 17.8, 14.9, 8.8, 3.7 Hz, 4H), 4.21 (dd, J = 8.6, 5.9 Hz, 1H), 3.84 – 3.73 (m, 2H), 3.69 (dd, J = 16.5, 5.6 Hz, 1H), 3.62 (s, 3H), 3.58 (s, 3H), 3.50 (tdd, J = 17.0, 10.3, 4.4 Hz, 2H), 3.07 (dd, J = 14.1, 4.6 Hz, 1H), 2.84 – 2.73 (m, 2H), 2.69 (dt, J = 13.5, 7.7 Hz, 1H), 2.31 (dt, J = 26.0, 8.3

Hz, 3H), 2.01 – 1.84 (m, 3H), 1.75 (dq, *J* = 13.6, 8.1 Hz, 1H), 1.38 (s, 9H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.84 (td, *J* = 10.7, 6.8 Hz, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{48}H_{77}O_{15}N_9NaS$, 1074.5152; found, 1074.5187.

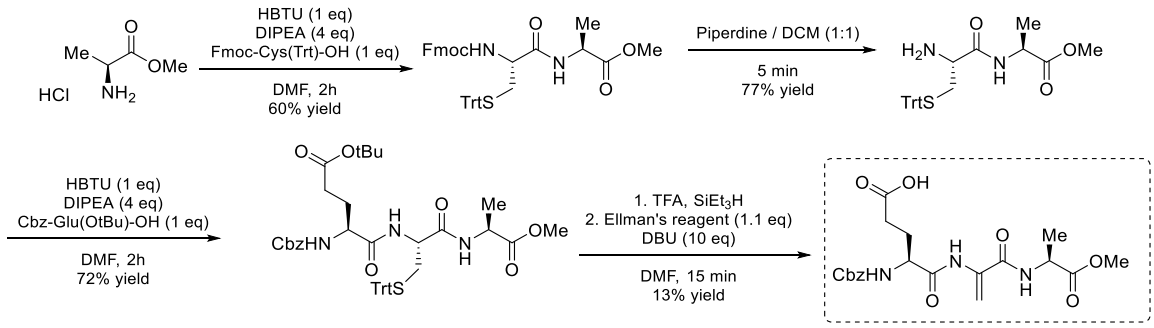


Boc-Val-Gly-Glu(OMe)-Ala-DHA-Val-Ser-Phe-Leu-OMe:

To a stirring solution of Boc-Val-Gly-Glu(OMe)-Ala-Cys-Val-Ser-Phe-Leu-OMe (230 mg, 0.22 mmol, 1.0 equiv) in degassed DMSO under N_2 was added dibromoethane (270 μL, 2.2 mmol, 10 equiv) and triethylamine (630 μL, 4.4 mmol, 20 equiv). The solution was allowed to continue stirring under N_2 for 14 hours. The resultant peptide was precipitated with 1M HCl (25 mL), collected by vacuum filtration, and washed with 1M HCl, water, and hexanes, providing the title compound as a white solid (190 mg, 85% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.33 (d, J = 6.8 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H), 8.09 – 8.06 (m, 2H), 8.01 (dd, J = 8.0, 2.0 Hz, 2H), 7.97 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 5.7 Hz, 4H), 7.17 (ddd, J = 6.6, 5.6, 2.7 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 6.06 (s, 1H), 5.57 (s, 1H), 5.00 (t, J = 5.4 Hz, 1H), 4.54 (td, J = 8.6, 4.7 Hz, 1H), 4.40 – 4.25 (m, 4H), 4.23 (dd, J = 8.7, 7.4 Hz, 1H), 3.83 – 3.73 (m, 2H), 3.70 (dd, J = 16.5, 5.6 Hz, 1H), 3.61 (s, 3H), 3.57 (s, 3H), 3.56 – 3.46 (m, 2H), 3.06 (dd, J = 14.0, 4.6 Hz, 1H), 2.80 (dd, J = 14.0, 9.0 Hz, 1H), 2.33 (t, J = 8.0 Hz, 2H), 2.03 (h, J = 6.9 Hz, 1H), 1.94 (ddd, J = 13.5, 7.9, 5.3 Hz, 2H), 1.76 (dq, J = 13.7, 8.1 Hz, 1H), 1.66 – 1.43 (m, 3H), 1.38 (s, 9H), 1.26 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.87 – 0.79 (m, 15H).

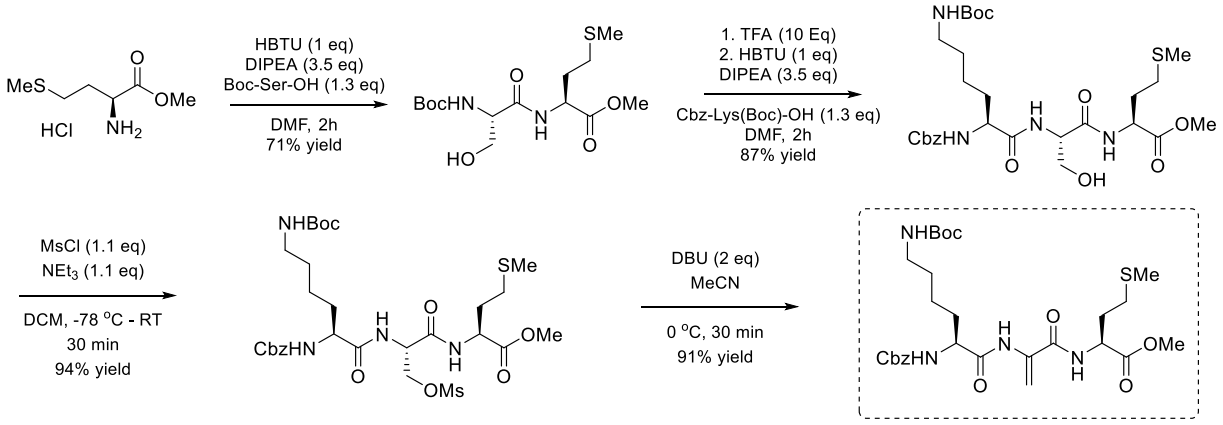
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{48}H_{75}O_{15}N_9Na$, 1040.5275; found, 1040.5261.



Scheme S2.3. Cbz-Glu-Dha-Ala-OMe: prepared by sequential peptide coupling and deprotection steps (beginning from the H_3N-Ala-OMe • HCl) following general procedure D to afford Cbz-Glu(OtBu)-Cys(Trt)-Ala-OMe. Cbz-Glu(OtBu)-Cys(Trt)-Ala-OMe (986 mg, 1.3 mmol, 1 equiv) was treated with TFA (3 mL), forming a dark yellow solution, and allowed to stir for 5 minutes until all solids were dissolved. To the stirring solution was added triethylsilane (0.3 mL) dropwise. All color faded from the mixture, and a white precipitate was observed. The mixture was concentrated by rotary evaporation and excess solvent was azeotropically removed with acetonitrile (3 x 20 mL). The flask was charged with Ellman's reagent (560 mg, 1.1 mmol, 1.1 equiv) and the solids were dissolved in DMF (10 mL). The mixture was allowed to stir for 10 minutes. To the stirring solution was added DBU (2 mL, 12.9 mmol, 10 equiv), forming a dark red solution, and allowed to stir for 15 additional minutes. The mixture was quenched with aqueous 1M HCl solution. The solution was partitioned between DCM (15 mL) and aqueous 1M HCl solution (25 mL), and the layers were separated. The aqueous layer was extracted with DCM (15 mL x 2), the organic layers were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by sequential flash column chromatography (5–10% MeOH/DCM + 2% acetic acid) and preparative HPLC (30 – 99% MeCN/H_2O, 0.1% TFA over 20 minutes) to afford the title compound (76 mg, 13% yield) as a clear colorless oil.

^{1}H NMR (600 MHz, Acetone-d_6) δ 8.96 (s, 1H), 8.05 – 7.99 (m, 1H), 7.43 – 7.30 (m, 5H), 6.92 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 5.61 (s, 1H), 5.17 – 5.09 (m, 2H), 4.54 (p, J = 7.3 Hz, 1H), 4.40 – 4.34 (m, 1H), 3.70 (s, 3H), 2.51 (t, J = 7.2 Hz, 2H), 2.29 – 2.21 (m, 1H), 2.04 – 1.99 (m, 1H), 1.44 (d, J = 7.3 Hz, 3H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{37}H_{42}N_3O_6$ 436.1714; found, 436.1723.

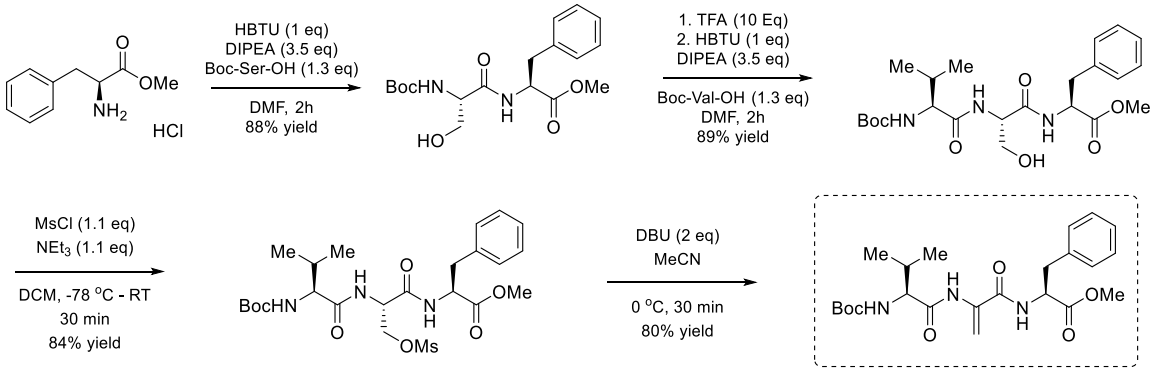


Scheme S2.4. Cbz-Lys(Boc)-Dha-Met-OMe: prepared by sequential peptide coupling and deprotection steps (beginning from the H_3N-Met-OMe • HCl) following general procedure D to afford Cbz-Lys(Boc)-Ser-Met-OMe. To a stirring solution of Cbz-Lys(Boc)-Ser-Met-OMe (312 mg, 0.5 mmol, 1 equiv) in DCM (20 mL) at –78 °C was added NEt_3 (72 μL, 0.55 mmol, 1.1 equiv) and methanesulfonyl chloride (42 μL, 0.55 mmol, 1.1 equiv). The mixture was allowed to warm to room temperature and stirred for an additional 30 minutes. The mixture was partitioned between DCM and aqueous NH_4Cl solution (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (25 mL x 2), the organic layers were combined, passed through a short pad of silica (flushed with EtOAc) to afford Cbz-Lys(Boc)-Ser(OMs)-Met-OMe (316 mg, 94% yield). To a stirring solution of Cbz-Lys(Boc)-Ser (OMs)-Met-OMe (250 mg, 0.37 mmol, 1 equiv) in MeCN (20 mL) at -20 °C was added DBU (112 μL, 0.74 mmol, 2.0 equiv). The mixture was allowed to stir for 30 minutes. The mixture was quenched with aqueous NH_4Cl solution (20 mL), MeCN was removed by rotary

evaporation. The solution was partitioned between DCM (25 mL) and aqueous NH_4Cl solution (50 mL), and the layers were separated. The aqueous layer was extracted with DCM (25 mL x 2), the organic layers were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (0–8% MeOH/DCM) to afford the title compound (200 mg, 91% yield) as a white crystalline solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.33 (d, J = 4.4 Hz, 4H), 7.29 (t, J = 4.4 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.45 (s, 1H), 5.60 – 5.56 (m, 1H), 5.37 (s, 1H), 5.14 – 5.04 (m, 2H), 4.74 (td, J = 7.3, 4.9 Hz, 1H), 4.60 (s, 1H), 4.23 (d, J = 7.1 Hz, 1H), 3.77 (d, J = 0.7 Hz, 3H), 3.07 (d, J = 6.8 Hz, 2H), 2.53 (t, J = 7.1 Hz, 2H), 2.19 (dtd, J = 14.6, 7.4, 5.0 Hz, 1H), 2.09 (s, 3H), 2.09 (s, 4H), 1.90 – 1.82 (m, 1H), 1.71 – 1.63 (m, 1H), 1.39 (s, 14H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{28}H_{43}O_8N_4S$, 595.2796; found, 595.2810.



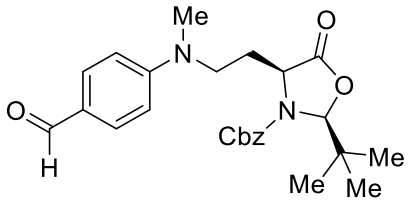
Scheme S2.5. Boc-Val-Dha-Phe-OMe: prepared by sequential peptide coupling and deprotection steps (beginning from the H_3N-Phe-OMe • HCl) following general procedure D to afford Boc-Val-Ser-Phe-OMe. To a stirring solution of Boc-Val-Ser-Phe-OMe (500 mg, 1.1 mmol, 1 equiv) in DCM (25 mL) at -78 °C was added NEt_3 (144 μL, 1.1 mmol, 1.1 equiv) and methanesulfonyl chloride (84 μL, 1.1 mmol, 1.1 equiv). The mixture was allowed to warm to room temperature and stirred for an additional 30 minutes. The mixture was partitioned between DCM and aqueous NH_4Cl

solution (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (25 mL x 2), the organic layers were combined, passed through a short pad of silica (flushed with 100% EtOAc) to afford Boc-Val-Ser(OMs)-Phe-OMe (488 mg, 84% yield). To a stirring solution of Boc-Val-Ser(OMs)-Phe-OMe (480 mg, 0.82 mmol, 1 equiv) in MeCN (25 mL) at –20 °C was added DBU (248 μL, 1.6 mmol, 2.0 equiv). The mixture was allowed to stir for 30 minutes. The mixture was quenched with aqueous NH_4Cl solution (20 mL), MeCN was removed by rotary evaporation. The solution was partitioned between DCM (25 mL) and aqueous NH_4Cl solution (50 mL), and the layers were separated. The aqueous layer was extracted with DCM (25 mL x 2), the organic layers were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (20–100% EtOAc/Hexanes) to afford the title compound (298 mg, 80% yield) as a white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.31 – 7.19 (m, 4H), 7.11 – 7.03 (m, 2H), 6.61 (d, J = 7.6 Hz, 1H), 6.45 (s, 1H), 5.21 – 5.14 (m, 1H), 5.05 (d, J = 8.6 Hz, 1H), 4.87 (dt, J = 7.7, 5.7 Hz, 1H), 4.08 (t, J = 7.1 Hz, 1H), 3.74 (s, 3H), 3.22 – 3.07 (m, 2H), 2.17 (d, J = 8.3 Hz, 1H), 1.43 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{23}H_{34}O_6N_3$, 448.2442; found, 448.2441.

2.4.5 Procedure and Characterization Data



1: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (59.7 mg, 0.2 mmol, 1 equiv), 4-(dimethylamino)benzaldehyde (89.4 mg, 0.6 mmol, 3 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.1 mg, 0.0020 mmol, 0.01 equiv) provided the

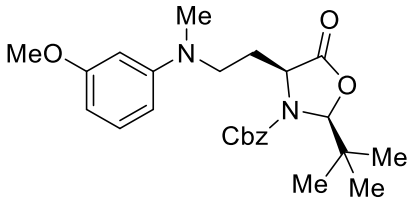
product as a single diastereomer (79 mg, 91% yield, >20:1 d.r. determined by NMR integral ratio) as a clear yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 20:3, then 20:4).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.71-7.67 (d, J = 8 Hz, 2H), 7.38–7.34 (m, 3H), 7.32–7.28 (m, 2H), 6.73–6.66 (d, J = 8 Hz, 2H), 5.57 (s, 1H), 5.12 (m, 2H), 4.25 (s, 1H), 3.77–3.64 (m, 2H), 2.96 (s, 3H), 2.20-2.08 (m, 2H), 0.96 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.15, 172.4, 153.2, 135.0, 132.1, 128.8, 128.78, 128.59, 125.50, 111.45, 111.0, 96.5, 68.6, 54.7, 49.9, 38.04, 37.07, 30.6, 24.8.

FTIR (neat) ν_{max}: 2969, 2911, 2360, 2342, 1787, 1717, 1664, 1593, 1557, 1526, 1497, 1481, 1467, 1456, 1439, 1388, 1369, 1336, 1312, 1300, 1288, 1230, 1194, 1166, 1113, 1068, 1040, 1011, 970, 943, 909, 869, 856, 835, 816, 785, 767, 728, 698, and 669 cm^-

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{25}H_{31}O_5N_2$, 439.2228; found, 439.2225.



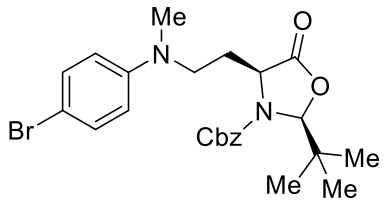
2: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (57.8 mg, 0.2 mmol, 1 equiv), 3-methoxy-N,-dimethylaniline (92.1 mg, 0.6 mmol, 3 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.3 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single diastereomer (71 mg, 81% yield, >20:1 d.r. determined by crude NMR analysis) as a clear colorless oil after purification by flash column chromatography (10 – 25% EtOAc/Hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 7.11 (t, J = 8.2 Hz 1H), 6.35 – 6.32 (m, 1H), 6.31 (t, J = 2.2 Hz, 1H), 6.28 (dd, J = 8.1, 2.3 Hz, 1H), 5.56 (s, 1H), 5.17 – 5.09 (m, 2H), 4.30 (m, 1H), 3.78 (s, 3H), 3.67-3.51 (m, 2H), 2.83 (s, 3H), 2.19-2.06 (m, 2H), 0.95 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 160.9, 155.7, 150.5, 135.2, 129.9, 128.7, 128.7, 128.6, 105.4, 101.7, 98.8, 96.4, 77.3, 68.4, 55.1, 54.8, 49.5, 37.9, 37.1, 30.5, 24.8.

FTIR (neat) ν_{max}: 2960, 1787, 1716, 1609, 1574, 1500, 1481, 1453, 1391, 1368, 1330, 1285, 1229, 1198, 1161, 1041, 1012, 971, 890, 823, 749, 697, 687, 636, and 579 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{25}H_{33}O_5N_2$, 441.2384; found, 441.2388.



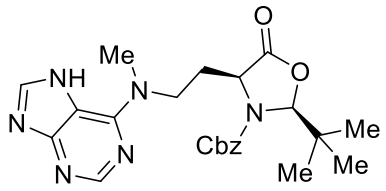
3: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (60 mg, 0.2 mmol, 1 equiv), 4-bromo-*N*,*N*-dimethylaniline (123 mg, 0.6 mmol, 3 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.4 mg, 0.002 mmol, 0.01 equiv) provided the product as a single diastereomer (85.3 mg, 84% yield, >20:1 d.r. determined by crude NMR analysis) as a clear colorless oil after purification by flash column chromatography (10% EtOAc/Hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 3H), 7.33-7.29 (m, 2H), 7.26 – 7.23 (d, J = 9 Hz, 2H), 6.56 (d, J = 8.2 Hz, 2H), 5.57 (s, 1H), 5.14 (s, 2H), 4.28 (m, 1H), 3.66-3.48 (m, 2H), 2.82 (s, 3H), 2.17 – 2.02 (m, 2H), 0. 96, (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 155.7, 148.0, 135.1, 131.9, 128.8, 128.8, 128.6, 114.0, 108.5, 96.4, 68.5, 54.7, 49.4, 37.9, 37.1, 30.4, 24.8.

FTIR (neat) ν_{max}: 2968, 2942, 2908, 2873, 1787, 1717, 1590, 1497, 1481, 1392, 1369, 1336, 1301, 1291, 1229, 1188, 1113, 1040, 1012, 971, 907, 807, 728, and 697 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{30}O_4N_2Br$, 489.1384; found, 489.1383.



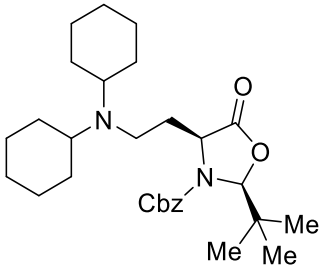
4: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (28.9 mg, 0.1 mmol, 1 equiv), N,N-dimethyladenine (270 ml, 0.5 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.1 mg, 0.001 mmol, 0.01 equiv) provided the product as a single diastereomer (72.9 mg, 88% yield, >20:1 d.r. determined by crude NMR analysis) as a white solid after purification by flash column chromatography (0 – 20% MeOH/DCM).

^{1}H NMR δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.83 (s, 1H), 7.30 (d, J = 3.2 Hz, 5H), 5.60 (d, J = 0.8 Hz, 1H), 5.19 – 5.12 (m, 2H), 4.49 (t, J = 7.3 Hz, 1H), 4.47 – 4.38 (m, 1H), 4.16 – 4.00 (m, 1H), 3.54 (s, 3H), 2.39 – 2.27 (m, 2H), 1.00 (s, 9H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 172.45, 155.97, 154.54, 151.52, 151.02, 136.79, 135.26, 128.64, 128.58, 128.35, 119.71, 96.65, 68.36, 55.38, 53.82, 37.04, 31.75, 29.29, 24.89.

FTIR (neat) ν_{max}: 3067, 2962, 2873, 2821, 2690, 1787, 1715, 1581, 1369, 1334, 1196, 910, and 729 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{29}O_4N_6$, 453.2245; found, 453.2250.



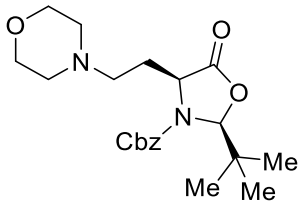
5: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), N-cyclohexyl-N-methylcyclohexanamine (130 μL, 0.6 mmol, 3.0 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.2 mg, 0.002 mmol, 0.01 equiv) provided the product as a single diastereomer (86 mg, 89% yield, >20:1 d.r. determined by crude NMR analysis) as a clear colorless oil after purification by flash column chromatography (5 – 20% EtOAc/Hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 5H), 5.55 (s, 1H), 5.18 (s, 2H), 4.36 (t, J = 7.1 Hz, 1H), 2.75 (ddt, J = 30.1, 14.5, 7.3 Hz, 2H), 2.49 (s, 2H), 1.97 – 1.88 (m, 2H), 1.75 – 1.52 (m, 10H), 1.27 – 1.14 (m, 10H), 0.96 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 155.9, 128.6, 128.5, 128.3, 96.2, 68.1, 58.0, 55.0, 43.0, 37.0, 32.1, 31.3, 26.4, 26.4, 26.2, 24.9.

FTIR (neat) ν_{max}: 2927, 2852, 1791, 1717, 1449, 1391, 1369, 1362, 1347, 1331, 1291, 1271, 1227, 1196, 1170, 1118, 1106, 1045, 1030, 1016, 977, 910, 891, 732, and 697 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{29}H_{45}O_4N_2$, 485.3374; found, 485.3367.



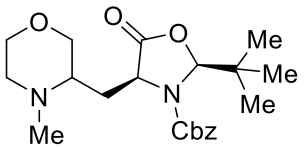
6: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), 4-methylmorpholine (66 μL, 0.6 mmol, 3 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.2 mg, 0.002 mmol, 0.01 equiv) provided the product as a single diastereomer (32 mg, 41% yield, >20:1 d.r. determined by crude NMR analysis) as a clear yellow oil after purification by flash column chromatography (70 – 95% EtOAc/Hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 5H), 7.23 (d, J = 8.9 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 5.56 (s, 1H), 5.18 – 5.09 (m, 2H), 4.33 (dd, J = 8.7, 5.4 Hz, 1H), 3.64 – 3.49 (m, 2H), 2.84 (s, 3H), 2.19 – 2.05 (m, 2H), 1.28 (s, 9H), 0.96 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 155.7, 146.9, 139.3, 135.2, 128.7, 128.6, 128.5, 126.0, 112.3, 96.4, 68.4, 54.9, 49.7, 38.0, 37.1, 33.7, 31.5, 30.6, 24.9.

FTIR (neat) ν_{max}: 2960, 2920, 2894, 2870, 2853, 2811, 1789, 1716, 1482, 1456, 1447, 1393, 1344, 1334, 1297, 1268, 1229, 1196, 1171, 1150, 1137, 1116, 1070, 1042, 1035, 1009, 971, 945, 916, 891, 861, 823, 801, 784, 764, 751, 698, and 665 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{21}H_{31}O_5N_2$, 391.2228; found, 391.2224.



6*: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), 4-methylmorpholine (66 μL, 0.6 mmol, 3

equiv), and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.2 mg, 0.002 mmol, 0.01 equiv) provided an inseparable 1:1 mixture of diastereomers (32 mg, 41% yield, 1:1 dr) as a clear yellow oil after purification by flash column chromatography (70 – 95% EtOAc/Hexanes).

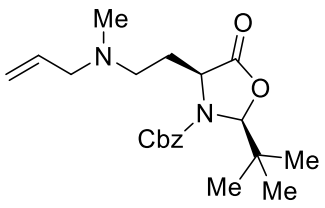
For the mixture of diastereomers:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 5H_{dr1} + 5H_{dr2}), 5.55 (s, 1H_{dr1} + 1H_{dr2}), 5.23 – 5.12 (m, 2H_{dr1} + 2H_{dr2}), 4.32 (s, 1H_{dr1} + 1H_{dr2}), 4.22 (s, 1H_{dr1} + 1H_{dr2}), 3.86 (m, 1H_{dr1} + 1H_{dr2}), 3.74 (m, 1H_{dr1} + 1H_{dr2}), 3.63 (m, 1H_{dr1} + 1H_{dr2}), 3.31 (m, 1H_{dr1} + 1H_{dr2}), 2.70 – 2.47 (m, 2H_{dr1} + 2H_{dr2}), 2.38 – 2.25 (m, 3H_{dr1} + 3H_{dr2}), 2.24 – 2.06 (m, 2H_{dr1} + 2H_{dr2}), 1.79 – 1.71 (m, 1H_{dr1} + 1H_{dr2}), 0.96 (s, 9H_{dr1} + 9H_{dr2}).

^{13}C NMR (150 MHz, $CDCl_3$) δ 13C NMR (151 MHz, CDCl3) δ 172.39, 172.30, 155.86, 155.68, 135.00, 134.94, 129.05, 128.97, 128.87, 128.82, 128.77, 128.75, 116.61, 112.65, 96.31, 96.23, 70.15, 70.04, 68.71, 68.62, 66.86, 66.43, 58.74, 55.37, 54.96, 53.82, 53.48, 42.59, 42.56, 40.62, 37.01, 37.00, 24.91, 24.86.

FTIR (neat) ν_{max}: 2960, 2852, 2798, 1790, 1718, 1456, 1482, 1393, 1345, 1323, 1282, 1229, 1121, 1033, 986, 892, 780, and 699 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{31}O_5N_2$, 391.2228; found, 391.2229.



7: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), N,N-dimethylallylamine (71 μl, 0.6 mmol,

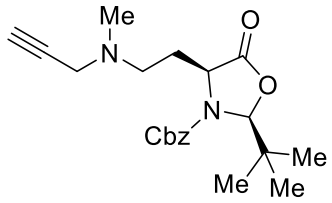
3.0 equiv), and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.2 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single diastereomer (61.4 mg, 82% yield, >20:1 d.r. determined by crude NMR analysis) as a clear yellow oil after purification by flash column chromatography (0 – 5% MeOH/DCM).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H), 5.80 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.55 (s, 1H), 5.20 – 5.07 (m, 4H), 4.46 (dd, J = 7.7, 6.5 Hz, 1H), 2.96 (dt, J = 13.7, 6.7 Hz, 2H), 2.66 (dt, J = 12.6, 8.0 Hz, 1H), 2.55 (dt, J = 13.2, 7.4 Hz, 1H), 2.15 (s, 3H), 2.02 (tdd, J = 7.8, 5.9, 2.2 Hz, 2H), 0.96 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 155.9, 135.5, 128.7, 128.6, 128.6, 128.5, 117.4, 96.2, 68.3, 60.7, 55.0, 53.4, 41.7, 37.0, 31.3, 24.9.

FTIR (neat) ν_{max}: 2971, 2961, 2912, 2874, 2794, 1790, 1716, 1498, 1482, 1456, 1392, 1369,1335, 1294, 1229, 1198, 1171, 1119, 1070, 1042, 1031, 1015, 971, 917, 893, 842, 825, 787, 775, 766, 751, 733, 697, and 664 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{24}H_{31}O_4N_2$, 375.2278; found, 375.2274.



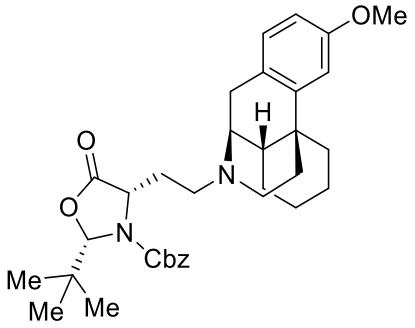
8: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), 3-dimethylamino-1-propyne (65 µl, 0.6 mmol, 3 equiv), and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.2 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single diastereomer (18 mg, 25% yield, >20:1 d.r. determined by crude NMR analysis) as a clear yellow oil after purification by flash column chromatography (15 – 45% EtOAc/Hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 5H), 5.57 (d, J = 7.9 Hz, 1H), 5.17 (s, 3H), 4.51 (t, J = 7.0 Hz, 1H), 3.28 (s, 2H), 2.72 (dt, J = 12.5, 7.8 Hz, 1H), 2.64 (d, J = 12.0 Hz, 1H), 2.24 (s, 3), 1.99 (tt, J = 7.5, 5.1 Hz, 2H), 0.96 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 155.9, 135.2, 128.7, 96.2, 78.3, 73.1, 68.4, 54.6, 53.9, 51.5, 45.1, 41.5, 40.9, 37.0, 31.3, 24.9.

FTIR (neat) ν_{max}: 3287, 2968, 2961, 2917, 2872, 2805, 2788, 1789, 1716, 1497, 1482, 1465,1456, 1393, 1369, 1361, 1344, 1334, 1309, 1291, 1269, 1229, 1198, 1179, 1118, 1073, 1041, 1015, 970, 934, 917, 893, 843, 827, 785, 765, 752, 698, and 675 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{31}O_4N_2$, 373.2122; found, 373.2117.



9: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (49 mg, 0.17 mmol, 1 equiv), dextromethorphan (232 mg, 0.85 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.4 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single diastereomer (61 mg, 64% yield, >20:1 d.r. determined by NMR analysis) as a yellow oil after purification by flash column chromatography (40 – 90% EtOAc/Hexanes).

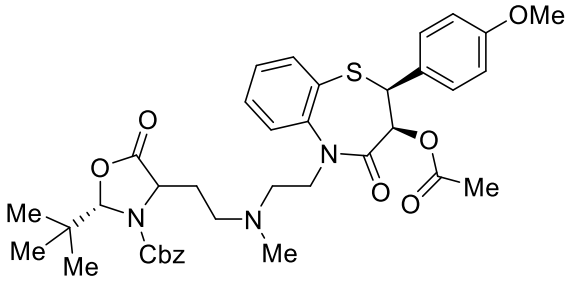
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 7.01 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 8.4, 2.6 Hz, 1H), 5.56 (s, 1H), 5.16 (d, J = 2.6 Hz, 2H), 4.48 (t, J = 6.8 Hz, 1H), 3.79 (s,

3H), 2.87 – 2.80 (m, 3H), 2.65 – 2.53 (m, 2H), 2.51 – 2.45 (m, 1H), 2.36 – 2.30 (m, 1H), 2.09 – 1.97 (m, 3H), 1.76 (d, J = 12.7 Hz, 1H), 1.71 – 1.59 (m, 1H), 1.53 – 1.47 (m, 1H), 1.37 – 1.24 (m, 6H), 1.13 – 1.03 (m, 1H), 0.96 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 158.2, 155.9, 141.9, 135.3, 129.9, 128.7, 128.6, 128.5, 128.4, 111.1, 110.6, 96.3, 77.2, 77.0, 76.8, 68.3, 56.4, 55.3, 55.2, 51.6, 45.2, 45.1, 42.0, 37.9, 37.1, 36.7, 32.0, 26.9, 26.6, 24.9, 24.7, 22.3.

FTIR (neat) ν_{max}: 2927, 2855, 1788, 1713, 1494, 1481, 1462, 1452, 1432, 1391, 1329, 1296, 1265, 1232, 1196, 1067, 1154, 1040, 970, 910, 852, 802, 784, 728, 696, 646, and 579 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{34}H_{45}O_5N_2$, 561.3323; found, 561.3323.



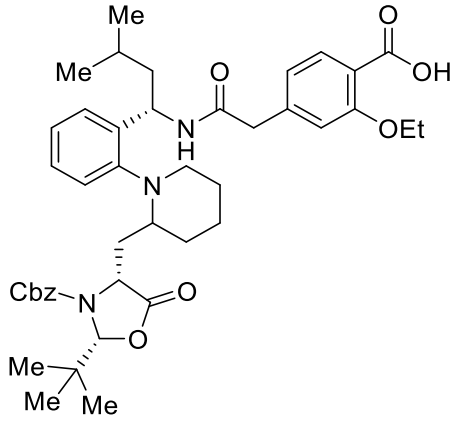
10: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (41 mg, 0.14 mmol, 1 equiv), diltiazem (293 mg, 0.71 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.7 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single diastereomer (62 mg, 62% yield, >20:1 d.r. determined by NMR analysis) in a combination of regioisomers (r.r. 93:7, 67% overall) after purification by flash column chromatography (20 – 80% EtOAc/Hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 7.4 Hz, 1H), 7.39 – 7.22 (m, 9H), 7.13 (t, J = 7.2 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 5.41 (s, 1H), 5.15 (d, J = 12.0 Hz, 1H), 5.09 – 5.05 (m, 2H), 4.97 – 4.93 (m, 2H), 4.29 (m, 1H), 3.74 (s, 3H), 3.59 (m, 1H), 2.65 (m, 3 H), 2.34 (s, 1H), 2.10, (s, 3H), 1.82 – 1.73 (m, 5H), 0.84 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 169.9, 166.8, 159.7, 155.7, 146.1, 135.4, 135.2, 131.0, 130.8, 128.7, 128.6, 128.6, 126.9, 126.7, 125.1, 113.8, 95.9, 71.1, 68.1, 56.2, 55.2, 54.5, 54.1, 53.5, 48.5, 42.3, 37.1, 31.0, 24.8, 20.5.

FTIR (neat) ν_{max}: 2960, 1788, 1711, 1678, 1609, 1584, 1513, 1444, 1394, 1360, 1296, 1220, 1199, 1180, 971, 918, 837,763, 735, 699, 663, 580, and 529 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{38}H_{46}O_8N_3S$, 704.3023; found, 704.3023



11: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (45 mg, 0.15 mmol, 1 equiv), repaglinide (339 mg, 0.75 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.9 mg, 0.0015 mmol, 0.01 equiv) provided an inseparable 1:1.1 mixture of diastereomers (79 mg, 71% yield, 1:1.1 d.r. determined by NMR integral ratio of the bolded resonances below) as a amber oil after purification by preparative HPLC (30 – 99% MeCN/H_2O, 0.1% TFA over 20 minutes).

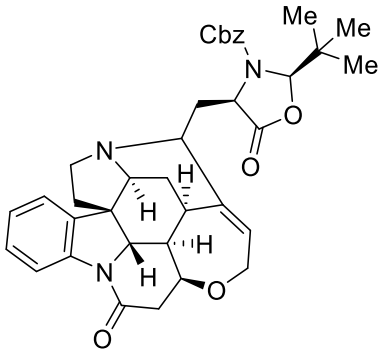
For the mixture of diastereomers:

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.96 (s, $1H_{dr1}$ + $1H_{dr2}$), **8.13 (d, *J* = 8.0 Hz, $1H_{dr1}$), 8.10 (d, *J* = 8.0 Hz, $1H_{dr2}$)**, 7.46 – 7.34 (m, $5H_{dr1}$ + $5H_{dr2}$), 7.25 – 6.59 (m, $6H_{dr1}$ + $6H_{dr2}$), 5.52 – 5.35 (m, $2H_{dr1}$ + $2H_{dr2}$), 5.25 – 5.09 (m, $2H_{dr1}$ + $2H_{dr2}$), 4.34 – 4.08 (m, $3H_{dr1}$ + $3H_{dr2}$), 3.61 – 3.45 (m, $2H_{dr1}$ + $2H_{dr2}$), 3.32 (s, $1H_{dr2}$), 3.17 – 2.95 (m, $1H_{dr1}$ + $1H_{dr2}$), 2.82 (s, $1H_{dr1}$), 2.65 (s, $1H_{dr2}$), 2.35 (s, $1H_{dr1}$), 2.22 – 1.92 (m, $1H_{dr1}$ + $1H_{dr2}$), 1.78 – 1.64 (m, $3H_{dr1}$ + $3H_{dr2}$), 1.62 – 1.45 (m, $7H_{dr1}$ + $7H_{dr2}$), 1.44 – 1.21 ($3H_{dr1}$ + $3H_{dr2}$), 0.96 – 0.84 (m, $6H_{dr1}$ + $6H_{dr2}$), **0.68 (s, $9H_{dr1}$), 0.64 (s, $9H_{dr2}$)**.

^{13}C NMR (150 MHz, $CDCl_3$) δ 13C NMR (151 MHz, CDCl3) δ 172.9, 172.0, 168.2, 167.8, 165.3, 157.5, 157.5, 156.3, 155.5, 150.1, 149.8, 143.2, 139.8, 135.2, 135.1, 133.9, 133.8, 129.0, 128.8, 128.7, 128.7, 128.6, 128.3, 128.1, 126.1, 125.6, 125.1, 123.8, 123.1, 122.8, 116.4, 113.8, 113.5, 96.8, 96.0, 68.7, 68.4, 66.1, 66.0, 58.3, 57.6, 54.8, 54.3, 49.7, 46.7, 46.6, 43.9, 43.7, 39.1, 37.6, 36.8, 36.6, 32.5, 32.3, 29.7, 26.8, 26.4, 25.3, 25.2, 24.6, 24.6, 22.9, 22.6, 22.5, 14.6, 14.6.

FTIR (neat) ν_{max}: 3270, 2955, 1788, 1712, 1649, 1535, 1238, 1194, 1167, 1110, 1034, 1016, 980, 750, 730, 700, 633, and 532 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{43}H_{56}O_8N_3$, 742.4062; found, 742.4067.



12: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58 mg, 0.2 mmol, 1 equiv), strychnine (337 mg, 1.0 mmol, 5 equiv), and

$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.5 mg, 0.002 mmol, 0.01 equiv) provided the product as a single diastereomer (48 mg, 38% yield, >20:1 d.r. determined by NMR analysis) as a white solid after purification by flash column chromatography (0 – 50% EtOAc/Hexanes).

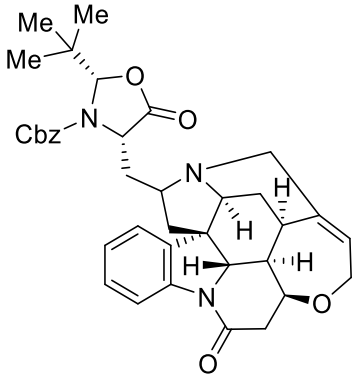
Mp: 248 °C (decomp.)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.27 – 7.24 (m, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 5.92 (s, 1H), 5.51 (s, 1H), 5.23 (s, 1H), 5.06 (s, 1H), 4.57 (s, 1H), 4.07 (s, 1H), 3.85 (m, 2H), 3.64 (s, 1H), 3.37 (m, 1H), 3.22 (m, 1H), 3.13-2.99 (m, 3H), 2.63 (dd, J = 16.4, 4.4 Hz, 1H), 2.30 (m, 1H), 1.87 (m, 1H), 1.71-1.56 (m, 3H), 1.34-1.17 (m, 3H), 0.95 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 170.3, 155.6, 141.6, 138.0, 134.1, 128.7, 128.6, 128.4, 128.0, 127.8, 127.7, 124.4, 122.0, 116.1, 95.9, 78.1, 72.8, 68.4, 64.6, 59.2, 54.6, 53.6, 53.3, 52.0, 46.3, 41.4, 40.2, 37.2, 32.8, 27.2, 25.6, 24.9.

FTIR (neat) ν_{max}: 3663, 2925, 2158, 1788, 1713, 1673, 1315, 1287, 159, 1085, 1045, 1017, 967, 885, 780, 754, 706, 681, 642, 624, and 541 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{37}H_{42}N_3O_6$ 624.3068; found, 624.3065.



12*: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58 mg, 0.2 mmol, 1 equiv), strychnine (337 mg, 1.0 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.5 mg, 0.002 mmol, 0.01 equiv) provided the product as a single diastereomer (48 mg, 39% yield, >20:1 d.r. determined by NMR analysis) as a white solid after purification by flash column chromatography (0 – 50% EtOAc/Hexanes) followed by subsequent by preparative HPLC (30 – 99% MeCN/H_2O, 0.1% TFA over 20 minutes).

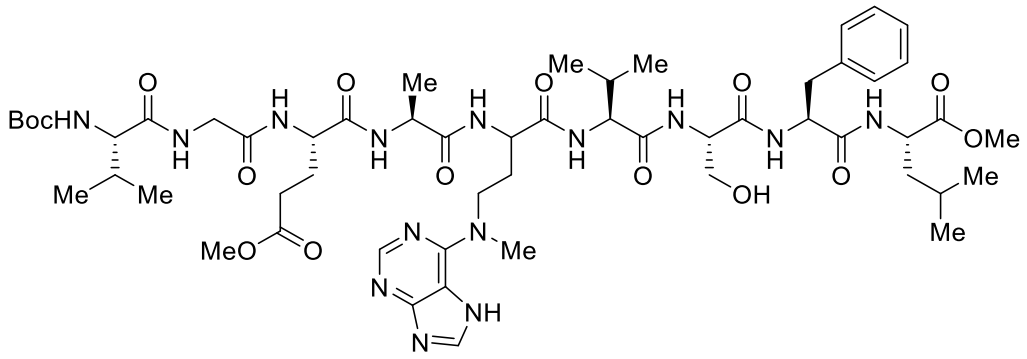
Mp: 176 °C (decomp.)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.16-6.97 (m, 6H), 5.88 (s, 1H), 5.48 (s, 1H), 5.05 (d, J = 11.4 Hz, 1H), 4.97 (d, J = 11.7 Hz, 1H), 4.19 (m, 1H), 4.07 (dd, J = 13.7, 6.8 Hz, 2H), 3.96 (dd, J = 13.6, 5.7 Hz, 1H), 3.88 (s, 1H), 3.78 (d, J = 10 Hz, 1H), 3.50 (d, J = 14.6 Hz, 1H), 3.23 (s, 1H), 3.06-3.02 (m, 2H), 2.68 (d, J = 14.6 Hz, 1H), 2.60 (d, J = 19.1, 1H), 2.23 (d, J = 14.3 Hz, 1H), 2.16 (t, J = 11.5 Hz, 1H), 1.89 (m, 2H), 1.33 (d, J = 14.2 Hz, 1H), 1.19-1.15 (m, 2H), 0.89 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 169.4, 155.6, 142.3, 140.1, 134.8, 132.3, 128.8, 128.6, 128.6, 127.6, 124.2, 122.3, 116.3, 96.3, 77.4, 68.5, 64.6, 60.3, 59.0, 56.0, 54.9, 52.5, 50.7, 48.7, 48.0, 42.4, 40.1, 37.1, 31.4, 29.7, 27.0, 24.8.

FTIR (neat) ν_{max}: 3661, 2919, 1664, 1649, 1631, 1596, 1461, 1390, 1227, 1097, 958, 836, 818, 781, 772, 751, 730, 697, 626, 578, 568, and 535 cm^{-1}.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{37}H_{42}N_3O_6$ 624.3068; found, 624.3067.



14: following the general procedure E, the reaction of Boc-Val-Gly-Glu(OMe)-Ala-DHA-Val-Ser-Phe-Leu-OMe (10 mg, 0.01 mmol, 1 equiv), N,N-dimethyladenine (8.2 mg, 0.05 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 mg, 0.00009 mmol, 0.01 equiv) provided a 3:1 mixture of diastereomers (6.4 mg, 54% yield, d.r. determined by NMR integral ratio) as a white solid after purification by preparative HPLC (30 – 99% $MeCN/H_2O$, 0.1% TFA over 20 minutes).

For the mixture of diastereomers:

^{1}H NMR Characteristic Signals (600 MHz, DMSO-d_6) δ 8.30 (d, J = 7.6 Hz, 1H), 8.21 (dd, J = 23.6, 17.2 Hz, 3H), 8.07 (q, J = 7.3, 6.6 Hz, 2H), 7.95 (dd, J = 19.8, 8.1 Hz, 2H), 7.20 (qt, J = 11.3, 4.2 Hz, 6H), 6.73 (d, J = 8.7 Hz, 1H), 4.55 (td, J = 8.5, 4.8 Hz, 1H), 4.40 – 4.22 (m, 6H), 3.82 – 3.77 (m, 2H), 3.70 (dd, J = 16.5, 5.5 Hz, 1H), 3.61 (s, 3H), 3.54 (s, 3H), 3.53 – 3.46 (m, 2H), 3.05 (dd, J = 14.0, 4.7 Hz, 1H), 2.80 (dd, J = 14.0, 8.6 Hz, 1H), 2.32 (t, J = 8.1 Hz, 1H), 1.93 (dh, J = 14.2, 7.4, 7.0 Hz, 3H), 1.81 – 1.68 (m, 1H), 1.66 – 1.44 (m, 2H), 1.37 (s, 9H), 1.27 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H), 0.86 – 0.76 (m, 12H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{55}H_{85}O_{15}N_{14}$, 1181.6308; found, 1181.6313.

Major Diastereomer ^{1}H NMR Characteristic Signals (600 MHz, DMSO-d_6) δ 7.10 (s, 1H), 7.01 (s, 1H), 1.27 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H).

Minor Diastereomer ^{1}H NMR Characteristic Signals (600 MHz, DMSO-d_6) δ 7.12 (s, 1H), 7.03 (s, 1H), 1.24 (d, J = 7.5 Hz, 3H), 0.75 (d, J = 7.6 Hz, 3H).

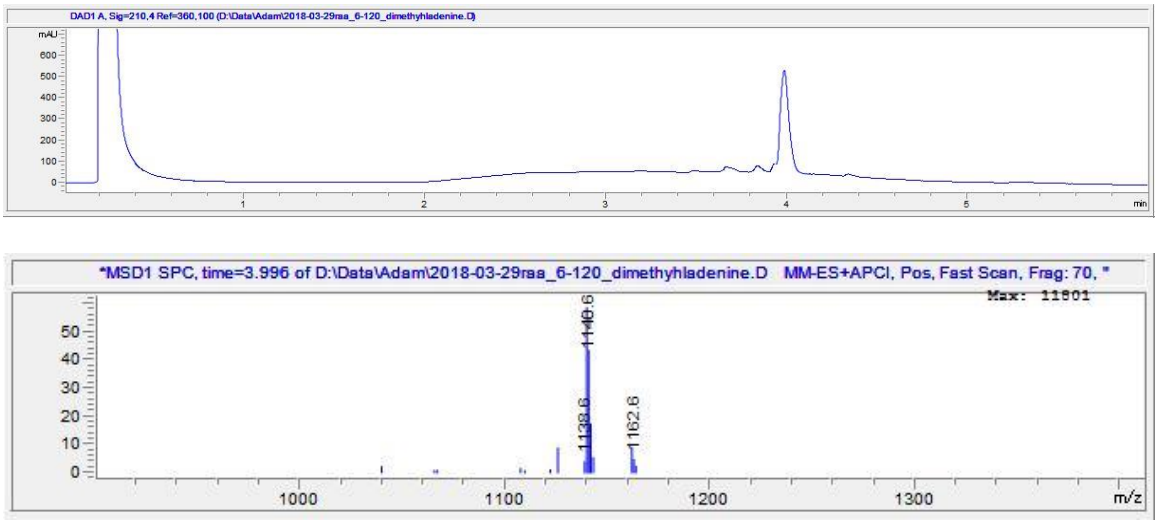
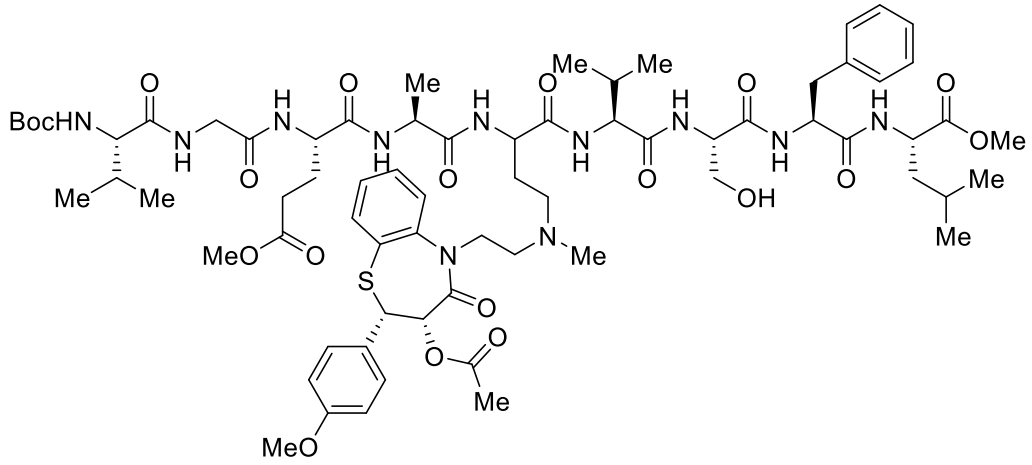


Figure S2.1. LCMS data for purified peptide **14**.



15: following the general procedure E, the reaction of Boc-Val-Gly-Glu(OMe)-Ala-DHA-Val-Ser-Phe-Leu-OMe (10 mg, 0.01 mmol, 1 equiv), diltiazem (20.7 mg, 0.05 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 mg, 0.00009 mmol, 0.01 equiv) provided the product (7.4 mg, 49% yield, 1.1:1 d.r. determined by NMR integral ratio of the bolded resonances below) as the TFA salt, a

white solid, after purification by preparative HPLC (30 – 99% MeCN/H_2O, 0.1% TFA over 20 minutes).

For the mixture of diastereomers:

^{1}H NMR characteristic signals (600 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.33 (d, J = 7.7 Hz, 1H), 8.13 (ddd, J = 31.2, 16.8, 8.1 Hz, 4H), 8.00 – 7.85 (m, 3H), 7.78 (d, J = 7.6 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.43 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 6.3 Hz, 4H), 7.19 – 7.14 (m, 1H), 6.94 – 6.90 (m, 2H), 6.87 (d, J = 8.8 Hz, 0H), 6.75 (d, J = 8.4 Hz, 1H), 5.18 (d, J = 7.7 Hz, 1H), 5.01 (d, J = 7.7 Hz, 1H), 4.56 (td, J = 8.4, 4.8 Hz, 1H), 4.48 (s, 1H), 4.38 (d, J = 6.8 Hz, 1H), 4.35 – 4.25 (m, 4H), 4.22 (q, J = 8.1, 7.6 Hz, 1H), 4.11 (s, 1H), 3.78 (s, 4H), 3.70 (dd, J = 16.5, 5.3 Hz, 1H), 3.62 (s, 3H), 3.56 (s, 3H), 3.55 – 3.48 (m, 2H), 3.06 (dd, J = 14.0, 4.7 Hz, 1H), 2.37 – 2.29 (m, 2H), 1.93 (dt, J = 15.1, 7.7 Hz, 3H), **1.84 (s, 3H)**, **1.76 (s, 3H)**, 1.63 – 1.45 (m, 2H), 1.38 (s, 9H), 1.24 (dd, J = 14.2, 7.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.84 (dt, J = 13.5, 6.9 Hz, 9H), 0.79 (t, J = 7.3 Hz, 3H), **0.76 – 0.69 (m, 3H$_{dr1}$, 3H$_{dr2}$)**.

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{70}H_{102}O_{19}N_{11}S$, 1432.7069; found, 1432.7044.

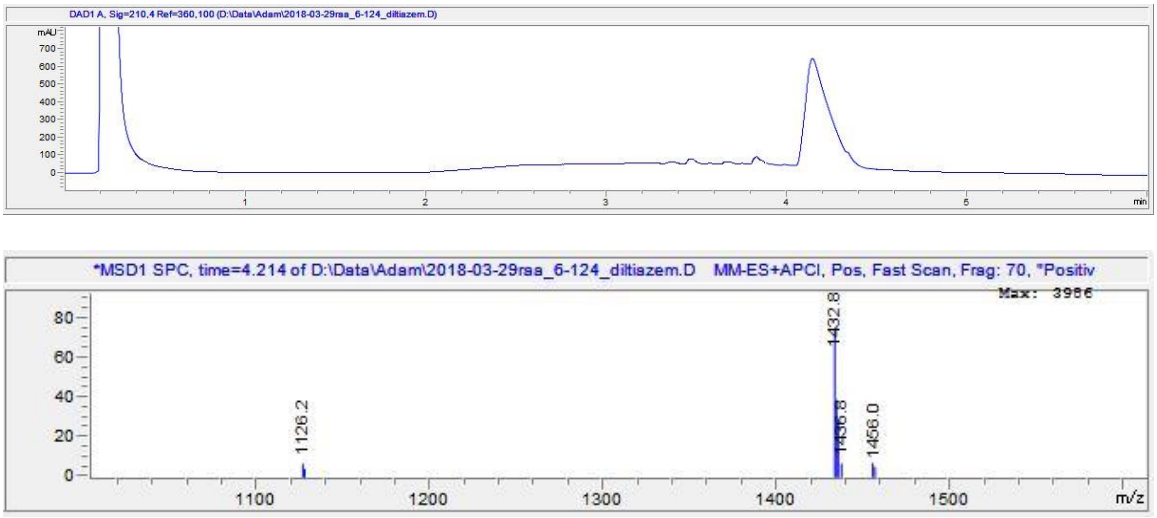
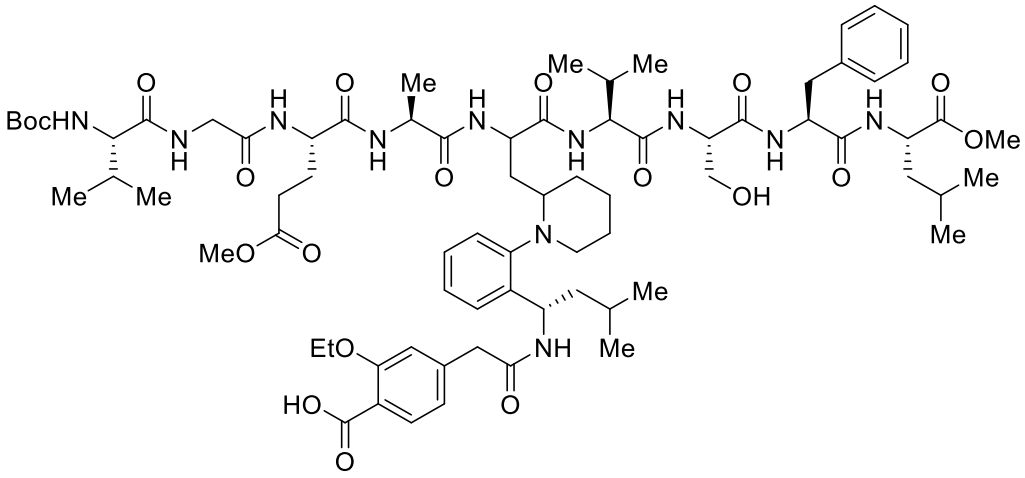


Figure S2.2. LCMS data for purified peptide **15**.



16: following the general procedure E, the reaction of Boc-Val-Gly-Glu(OMe)-Ala-DHA-Val-Ser-Phe-Leu-OMe (10 mg, 0.01 mmol, 1 equiv), repaglinide (22.6 mg, 0.05 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 mg, 0.00009 mmol, 0.01 equiv) provided a mixture of four diastereomers over four fractions (6.0 mg, 41% yield, 1:2:2:2 d.r. determined by HPLC integral ratio) as a white solid after purification by preparative HPLC (30 – 99% MeCN/H_2O, 0.1% TFA over 20 minutes).

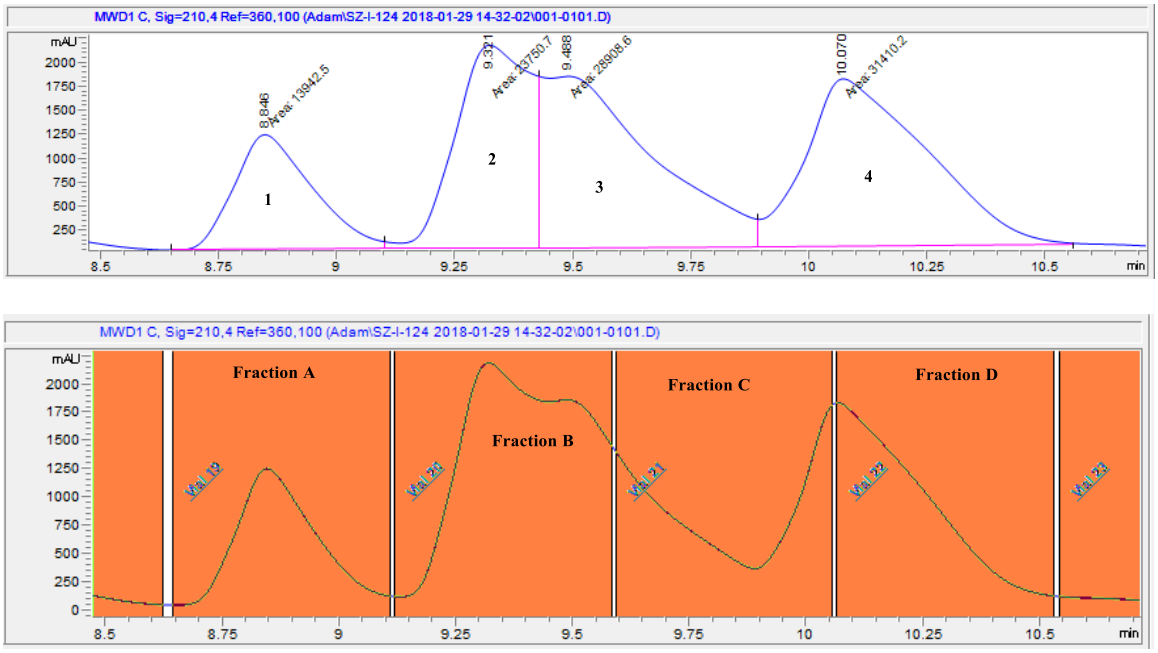


Figure S2.3. LCMS data for crude peptide **16**.

Fraction A: Diastereomer 1

^{1}H NMR Characteristic Signals (600 MHz, DMSO-d_6) δ 8.07 (s, 4H), 8.02 (s, 4H), 7.97 – 7.88 (m,5), 7.54 (d, J = 7.9 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 8.9 Hz, 1H), 4.53 (d, J = 4.7 Hz, 2H), 4.32 (t, J = 7.1 Hz, 2H), 4.27 (t, J = 6.2 Hz, 2H), 4.17 (s, 2H), 4.01 (q, J = 7.0 Hz,3), 3.80 (s, 1H), 3.61 (s, 3H), 3.55 (s, 3H), 3.05 (d, J = 14.3 Hz, 1H), 2.79 (dd, J = 13.8, 8.6 Hz,2), 1.98 – 1.45 (m, 15H), 1.38 (s, 9H), 1.32 (t, J = 7.0 Hz, 2H), 0.93 – 0.75 (m, 24H), 0.70 (d, J = 6.7 Hz, 2H), 0.66 (d, J = 6.8 Hz, 2H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{75}H_{112}O_{19}N_{11}$, 1470.8131; found, 1470.8099.

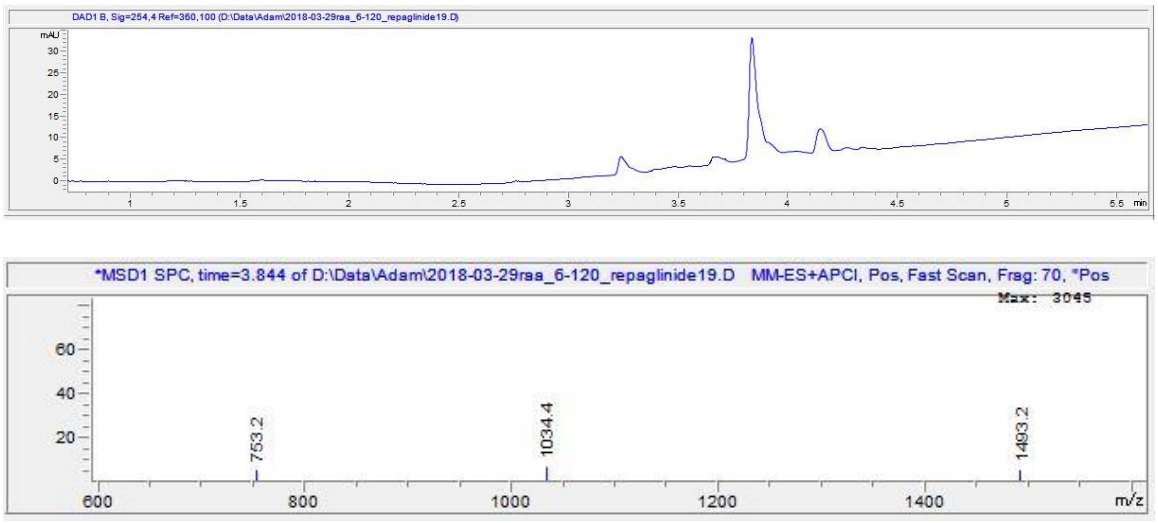


Figure S2.4. LCMS data for purified peptide **16** diastereomer 1.

Fraction B: Diastereomers 2 and 3

For the mixture of diastereomers:

^{1}H NMR Characteristic Signals ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.43 (d, J = 8.3 Hz, 1H$_{dr2}$), 8.28 (d, J = 7.7 Hz, 1H$_{dr2}$ + 1H$_{dr3}$), 8.18 – 7.96 (m, 5H$_{dr2}$ + 5H$_{dr3}$), 7.94 – 7.78 (m, 2H$_{dr2}$ + 2H$_{dr3}$), 7.55 – 7.50 (m, 1H$_{dr2}$ + 1H$_{dr3}$), 7.35 (d, J = 8.0 Hz, 1H$_{dr3}$), 7.29 – 7.26 (m, 1H$_{dr2}$), 7.26 – 7.15 (m, 8H$_{dr2}$ + 8H$_{dr3}$), 7.13 – 7.07 (m, 1H$_{dr2}$ + 1H$_{dr3}$), 7.05 – 6.94 (m, 3H$_{dr2}$ + 3H$_{dr3}$), 6.83 (d, J = 7.8 Hz, 1H$_{dr2}$ + 1H$_{dr3}$), 6.72 (d, J = 8.9 Hz, 1H$_{dr2}$ + 1H$_{dr3}$), 4.54 (td, J = 8.5, 4.7 Hz, 1H$_{dr2}$ + 2H$_{dr3}$), 4.46 (m, 1H$_{dr2}$), 4.37 – 4.18 (m, 6H), 4.06 – 3.94 (m, 3H$_{dr2}$ + 3H$_{dr3}$), 3.84 – 3.63 (m, 6H$_{dr2}$ + 6H$_{dr3}$), 3.62 (s, 3H$_{dr2}$), 3.61 (s, 3H$_{dr3}$), 3.56 (s, 3H$_{dr2}$), 3.55 (s, 1H$_{dr3}$), 3.53 – 3.40 (m, 5H$_{dr2}$ + 5H$_{dr3}$), 3.32 (d, J = 13.4 Hz, 1H$_{dr3}$), 3.23 (d, J = 10.8 Hz, 1H$_{dr2}$), 3.10 – 2.98 (m, 1H$_{dr2}$ + 1H$_{dr3}$), 2.87 – 2.72 (m, 2H$_{dr2}$ + 2H$_{dr3}$), 2.35 – 2.27 (m, 3H$_{dr2}$ + 3H$_{dr3}$), 2.22 – 2.11 (m, 1H$_{dr2}$ + 1H$_{dr3}$), 1.99 – 1.81 (m, 4H$_{dr2}$ + 4H$_{dr3}$), 1.77 – 1.65 (m, 3H$_{dr2}$ + 3H$_{dr3}$), 1.65 – 1.41 (m, 8H$_{dr2}$ + 8H$_{dr3}$), 1.38 (s, 9H$_{dr3}$), 1.37 (s, 9H$_{dr2}$), 1.33 – 1.30 (m, 4H$_{dr2}$ + 4H$_{dr3}$), 1.10 (d, J = 7.1 Hz, 4H$_{dr2}$ + 4H$_{dr3}$), 0.94 – 0.78 (m, 24H$_{dr2}$ + 24H$_{dr3}$), 0.76 (d, J = 6.6 Hz, 2H$_{dr2}$ + 2H$_{dr3}$), 0.69 (d, J = 6.6 Hz, 1H$_{dr2}$ + 1H$_{dr3}$), 0.64 (d, J = 6.7 Hz, 1H$_{dr2}$ + 1H$_{dr3}$).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{75}H_{112}O_{19}N_{11}$, 1470.8131; found, 1470.8095.

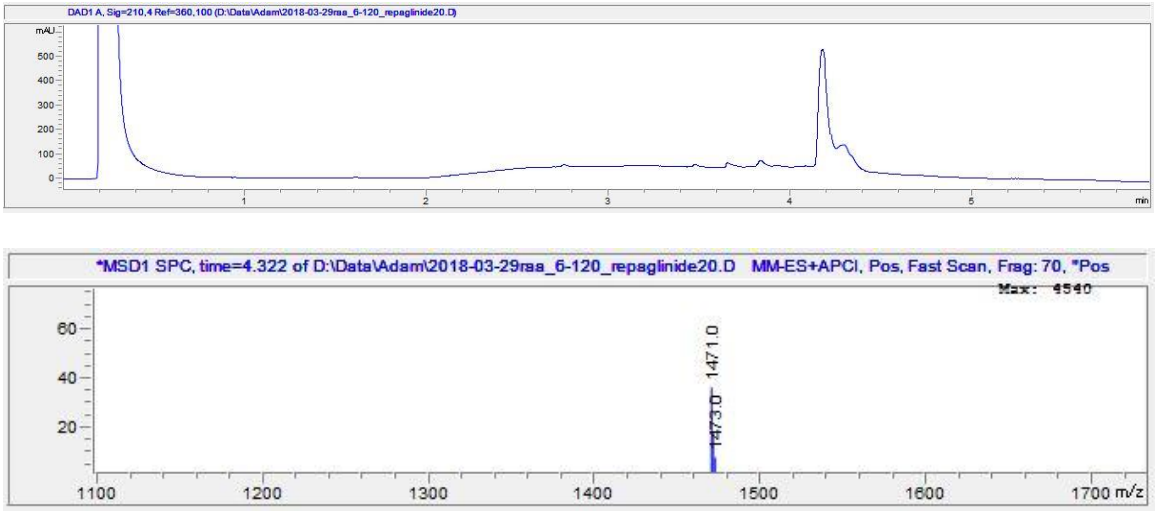


Figure S2.5. LCMS data for crude peptide **16** diastereomer 2 and 3.

Fraction C: Diastereomers 2, 3, and 4

For the mixture of diastereomers:

^{1}H NMR Characteristic Signals ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.28 (d, J = 7.6 Hz, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 8.15 (d, J = 8.9 Hz, $1H_{dr2}$ + $1H_{dr3}$), 8.07 (s, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 8.01 – 7.88 (m, $3H_{dr2}$ + $3H_{dr3}$ + $4H_{dr4}$), 7.82 (d, J = 9.2 Hz, $1H_{dr2}$ + $1H_{dr3}$), 7.58 – 753 ($1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 7.36 (d, J = 7.5 Hz, $1H_{dr3}$ + $1H_{dr4}$), 7.26 – 7.14 (m, $8H_{dr2}$ + $8H_{dr3}$ + $8H_{dr4}$), 7.05 – 6.98 (m, $2H_{dr2}$ + $2H_{dr3}$ + $2H_{dr4}$), 6.88 – 6.82 (m, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 6.72 (d, J = 8.6 Hz, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 4.57 – 4.50 (m, $1H_{drB2}$ + $1H_{dr3}$ + $1H_{dr4}$), 4.36 – 4.24 (m, $4H_{dr2}$ + $4H_{dr3}$ + $4H_{dr4}$), 4.08 – 3.98 (m, $2H_{dr2}$ + $2H_{dr3}$ + $2H_{dr4}$), 3.82 – 3.92(m, $2H_{dr2}$ + $2H_{dr3}$ + $2H_{dr4}$), 3.61 (s, $3H_{dr2}$), 3.61 (s, $3H_{dr4}$), 3.61 (s, $3H_{dr3}$), 3.57 (s, $3H_{dr4}$), 3.56 (s, $3H_{dr2}$), 3.55 (s, $3H_{dr3}$), 3.11 – 2.99 (m, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 2.83 – 2.75 (m, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 2.34 – 2.28 (m, $1H_{dr2}$ + $1H_{dr3}$ + $1H_{dr4}$), 1.97 – 1.65 (m, $2H_{dr2}$ + $2H_{dr3}$ + $2H_{dr4}$), 1.65 – 1.41 (m, $3H_{dr2}$ + $4H_{dr3}$ + $4H_{dr4}$), 1.39 – 1.37 (m, $9H_{dr2}$ + $9H_{dr3}$ + $9H_{dr4}$), 1.35 – 1.30 (m, 2.4 Hz, $3H_{dr2}$ + $3H_{dr3}$ + $3H_{dr4}$),

1.28 – 1.19 (m, $5H_{dr2}$ + $5H_{dr3}$ + $5H_{dr4}$), 0.92 – 0.77 (m, $24H_{dr2}$ + $24H_{dr3}$ + $24H_{dr4}$), 0.72 – 0.60 (m, $4H_{dr2}$ + $4H_{dr3}$ + $4H_{dr4}$).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{75}H_{112}O_{19}N_{11}$, 1470.8131; found, 1470.8094.

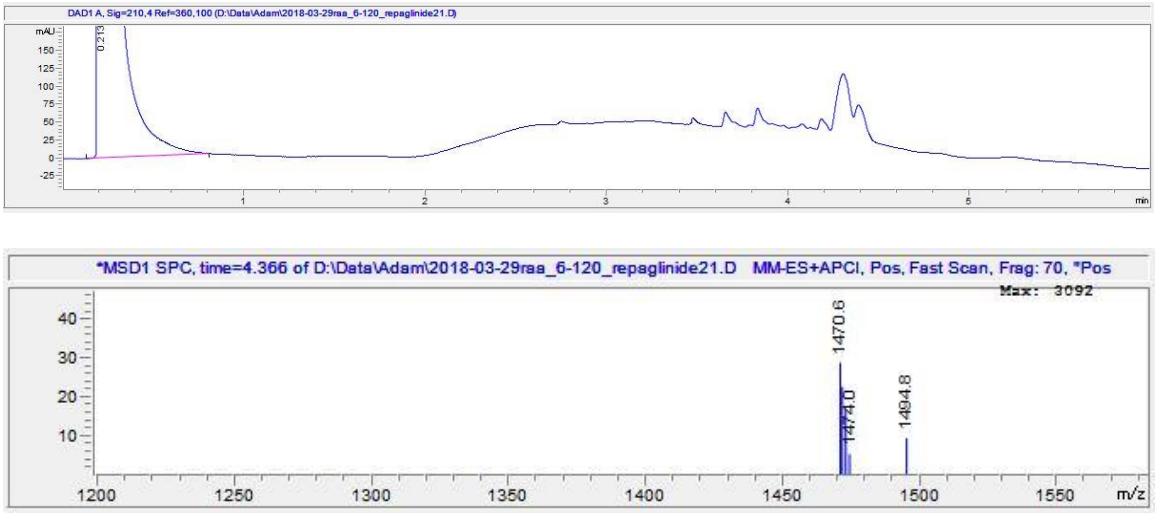


Figure S2.6. LCMS data for crude peptide **16** diastereomer 2, 3, and 4.

Fraction D: Diastereomer 4

^{1}H NMR Characteristic Signals (600 MHz, DMSO-d_6) δ 8.28 (d, *J* = 7.5 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.99 – 7.87 (m, 3H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 3.5 Hz, 4H), 7.17 (d, *J* = 5.0 Hz, 2H), 7.13 – 7.04 (m, 3H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.58 – 4.49 (m, 1H), 4.35 – 4.24 (m, 3H), 4.20 (t, *J* = 7.2 Hz, 1H), 4.17 – 4.13 (m, 1H), 4.04 (d, *J* = 7.8 Hz, 3H), 3.82 – 3.72 (m, 2H), 3.67 (dd, *J* = 16.5, 5.6 Hz, 1H), 3.61 (s, 3H), 3.57 (s, 3H), 3.07 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.80 (dd, *J* = 14.1, 8.8 Hz, 1H), 2.31 (t, *J* = 8.1 Hz, 2H), 1.96 – 1.82 (m, 2H), 1.72 (dd, *J* = 14.1, 7.4 Hz, 1H), 1.63 – 1.45 (m, 3H), 1.38 (s, 9H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 15.0 Hz, 2H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.93 – 0.78 (m, 18H), 0.75 – 0.65 (m, 4H).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{75}H_{112}O_{19}N_{11}$, 1470.8131; found, 1470.8096.

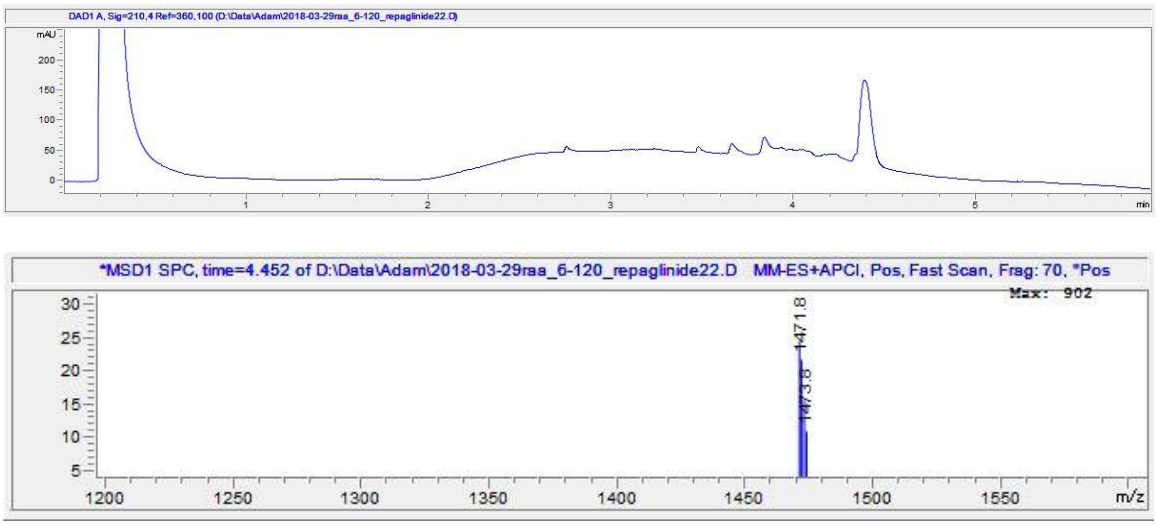
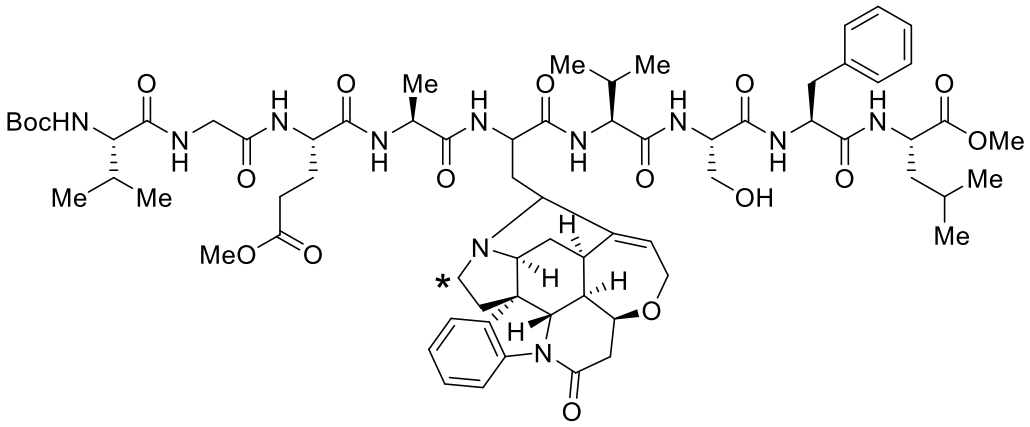


Figure S2.7. LCMS data for purified peptide **16** diastereomer 4.



17: following the general procedure E, the reaction of **Boc-Val-Gly-Glu(OMe)-Ala-Dha-Val-Ser-Phe-Leu-OMe** (10 mg, 0.01 mmol, 1 equiv), strychnine (17 mg, 0.05 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 mg, 0.00009 mmol, 0.01 equiv) provided a mixture of regioisomers as the TFA salt (8.4 mg, 58% yield), a white solid after purification by preparative HPLC (30 – 99% $MeCN/H_2O$, 0.1% TFA over 20 minutes).

^{1}H NMR Characteristic Signals (600 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.28 – 8.17 (m), 8.16 – 7.98 (m), 7.97 – 7.77 (m,), 7.50 – 7.34 (m), 7.30 – 7.21 (m), 7.19 – 7.07 (m), 7.06 – 6.93 (m), 6.71 – 6.57 (m, 1H), 6.34 – 6.17 (m, 1H), 4.63 – 4.56 (m), 4.51 – 4.42 (m), 4.35 – 3.58 (m), 3.55 – 3.52 (m), 3.51 – 3.46 (m), 3.46 – 3.37 (m), 3.37 – 3.22 (m), 3.17 – 3.03 (m), 3.02 – 2.82 (m), 2.79 – 2.69 (m), 2.30 – 2.19 (m), 2.18 – 2.02 (m), 2.02 – 1.93 (m), 1.91 – 1.76 (m), 1.72 – 1.64 (m), 1.62 – 1.35 (m), 1.31 (s, 9H), 1.24 – 1.18 (m, 3H), 1.18 – 1.08 (m), 0.83 – 0.73 (m, 12H), 0.73 – 0.68 (m, 3H), 0.68 – 0.62 (m, 3H).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{69}H_{98}O_{17}N_{11}$, 1352.7137; found, 1352.7115.

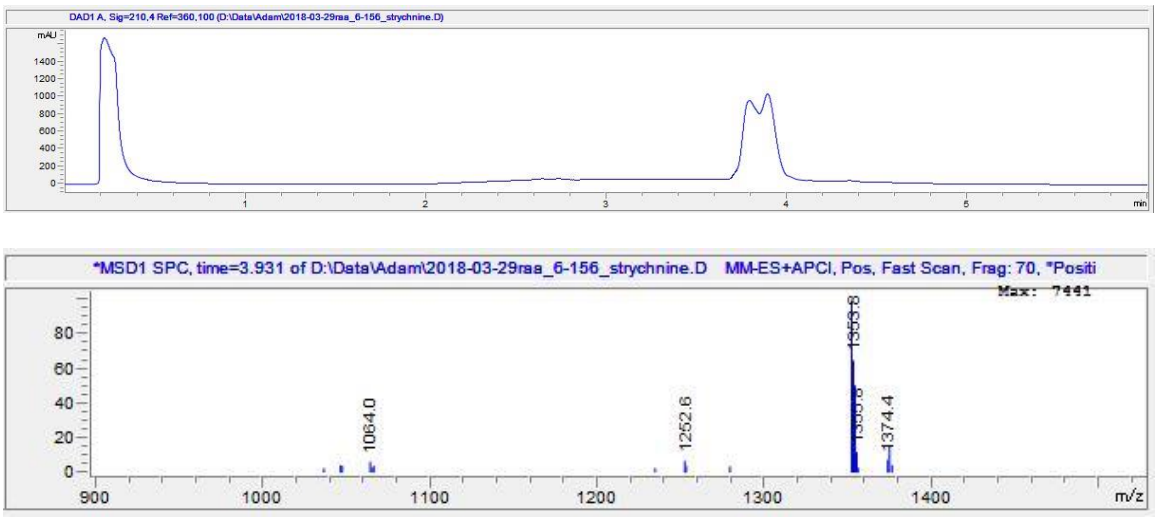
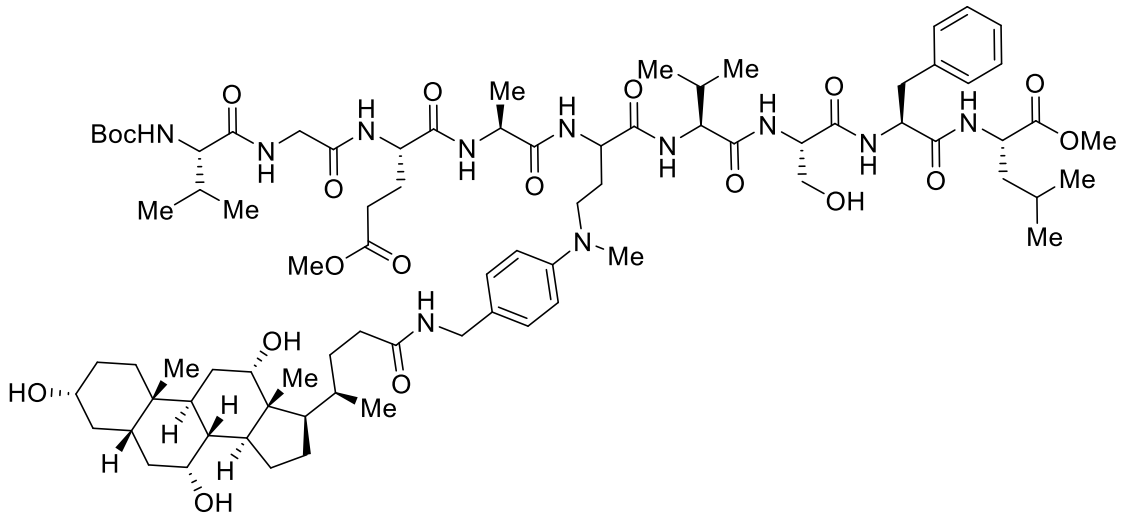


Figure S2.8. LCMS data for purified peptide **17**.



18: following the general procedure E, the reaction of Boc-Val-Gly-Glu(OMe)-Ala-DHA-Val-Ser-Phe-Leu-OMe (10 mg, 0.01 mmol, 1 equiv), aniline-tethered cholic acid (27.1 mg, 0.05 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 mg, 0.009 mmol, 0.1 equiv) provided a mixture of diastereomers (8.5 mg, 54% yield, 2:1 d.r. determined by NMR integral ratio) as a white solid after purification by preparative HPLC (30 – 99% $MeCN/H_2O$, 0.1% TFA over 20 minutes).

For the mixture of diastereomers:

^{1}H NMR characteristic signals ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.08 (t, J = 8.6 Hz, 1H), 8.04 – 7.97 (m, 2H), 7.87 (dd, J = 24.0, 8.3 Hz, 1H), 7.79 (d, J = 9.0 Hz, 0H), 6.64 (d, J = 8.6 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.48 (td, J = 8.4, 4.8 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.29 – 4.12 (m, 4H), 4.03 (d, J = 5.6 Hz, 2H), 3.76 – 3.69 (m, 2H), 3.54 (s, 3H), 3.49 (s, 3H), 2.99 (dd, J = 14.0, 4.8 Hz, 1H), 2.73 (s, 2H), 1.95 – 1.79 (m, 6H), 1.23 – 1.13 (m, 6H), 0.86 (d, J = 6.4 Hz, 2H), 0.81 (d, J = 6.5 Hz, 3H), 0.79 – 0.73 (m, 9H), 0.55 – 0.45 (m, 3H).

Major diastereomer characteristic signals: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.22 (d, J = 7.7 Hz, 1H), 1.30 (s, 9H), 0.71 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H), 0.51 – 0.48 (m, 3H).

Minor diastereomer characteristic signals: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.20 (d, J = 7.6 Hz, 1H), 1.29 (s, 10H), 0.72 (s, 3H), 0.68 (d, J = 6.8 Hz, 3H), 0.51 (s, 3H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{81}H_{128}O_{19}N_{11}$, 1558.9383; found, 1558.9392.

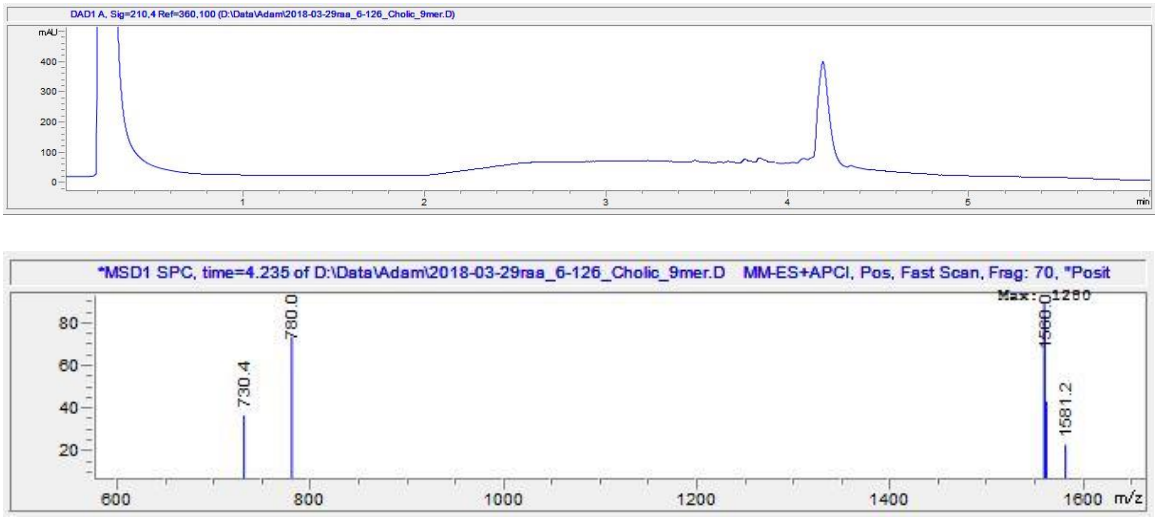
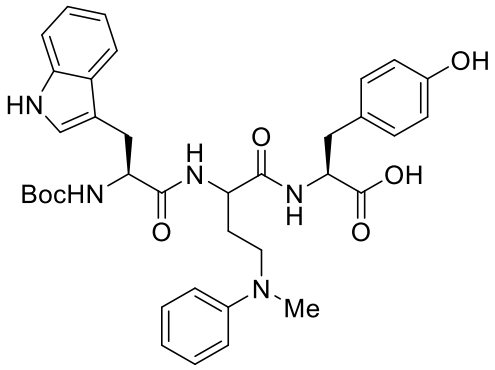


Figure S2.9. LCMS data for purified peptide **18**.



19: following the general procedure B, the reaction of Boc-Trp-Dha-Tyr-OH (26 mg, 0.05 mmol, 1 equiv), N,N-dimethylaniline (30 μL, 0.25 mmol, 5 equiv), and $[Ir(ppy)_2(dtbbpy)]PF_6$ (0.5 mg, 0.0005 mmol, 0.01 equiv) provided an inseparable mixture of diastereomers of the product (28 mg, 86% yield, 1.2:1 d.r. determined by NMR integral ratio of the bolded resonances below) as a white solid after purification by flash column chromatography (0 – 20% MeOH/DCM).

For the mixture of diastereomers:

^{1}H NMR (600 MHz, MeOD δ 7.59 (d, *J* = 7.8 Hz, $7H_{dr1} + 7H_{dr2}$), 7.31 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.17 – 6.95 (m, $4H_{dr1} + 4H_{dr2}$), 6.72 – 6.50 (m, $3H_{dr1} + 3H_{dr2}$), 4.47 – 4.14 (m, $3H_{dr1} + 3H_{dr2}$), 3.58 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.51 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.26 – 3.16 (m, 2H), 3.13 – 3.03 (m, $2H_{dr1} + 2H_{dr2}$), 2.92 – 2.83 (m, $1H_{dr1} + 1H_{dr2}$), **2.79 (s, 3H)**, 2.73 – 2.66 (m, $1H_{dr1} + 1H_{dr2}$), **2.63 (s, 3H)**, 1.71 (m, $1H_{dr1} + 1H_{dr2}$, **1.37 (s, 9H), 1.34 (s, 9H)**

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{36}H_{44}O_7N_5$, 658.3235; found, 658.3229.

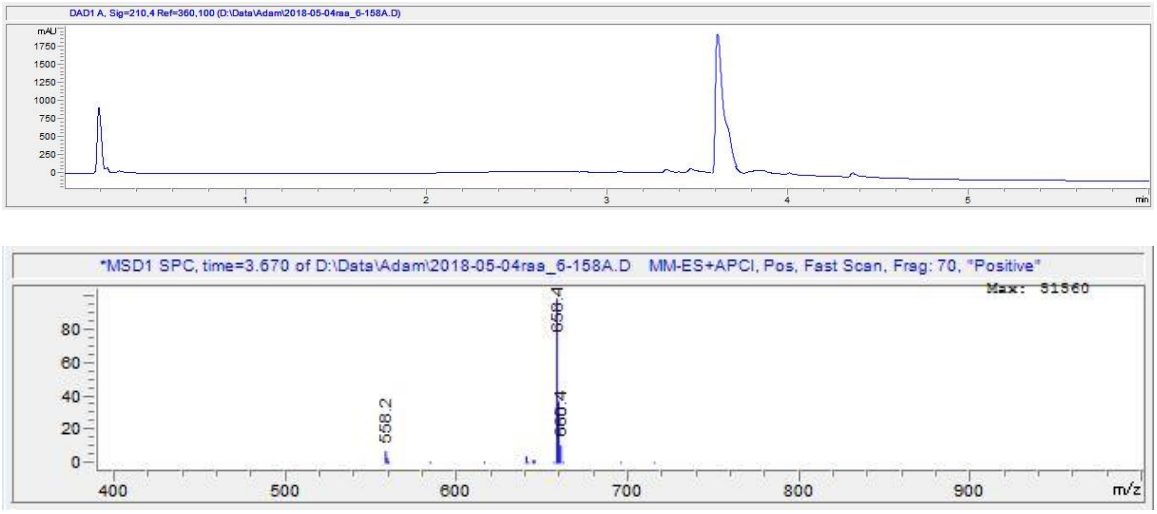
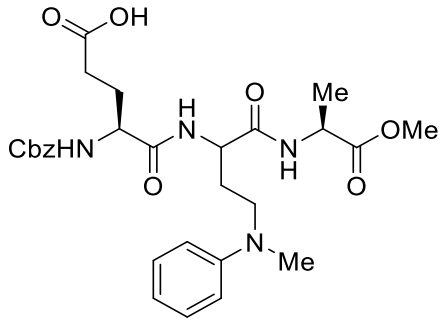


Figure S2.10. LCMS data for purified peptide **19**.



20: following the general procedure B, the reaction of Cbz-Glu-Dha-Ala-OMe (20.2 mg, 0.05 mmol, 1 equiv), N,N-dimethylaniline (29.4 μL, 0.25 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.5 mg, 0.0005 mmol, 0.01 equiv) provided an inseparable mixture of diastereomers of the product (12.8 mg, 50% yield, 1:1 d.r. determined by NMR integral ratio of the bolded resonances below) as a blue oil after purification by preparative HPLC (30 – 99% $MeCN/H_2O$, 0.1% TFA over 20 minutes).

For the mixture of diastereomers:

^{1}H NMR (600 MHz, MeOD) δ 7.53 – 7.49 (m, $2H_{dr1}$ + $2H_{dr2}$), 7.44 – 7.42 (m, $1H_{dr1}$ + $1H_{dr2}$), 7.39 – 7.26 (m, $7H_{dr1}$ + $7H_{dr2}$), 5.09 (s, $2H_{dr1}$ + $2H_{dr2}$), 4.49 (m, $1H_{dr1}$ + $1H_{dr2}$), 4.38 (dq, J = 14.5, 7.3 Hz, $1H_{dr1}$ + $1H_{dr2}$), **4.09 (m, $1H_{dr1}$)**, **4.05 (m, $1H_{dr2}$)**, 3.71 (s, $3H_{dr1}$), 3.70 (s, $3H_{dr2}$), 3.68 – 3.56 (m, $2H_{dr1}$ + $2H_{dr2}$), **3.18 (s, $3H_{dr1}$), 3.16 (s, $3H_{dr2}$)**, 2.45 – 2.36 (m, $2H_{dr1}$ + $2H_{dr2}$), 2.17 – 1.97 (m, $3H_{dr1}$ + $3H_{dr2}$), 1.89 – 1.83 (m, $1H_{dr1}$ + $1H_{dr2}$), **1.38 (d, J = 7.3 Hz, $3H_{dr1}$), 1.36 (d, J = 7.3 Hz, $3H_{dr1}$)**.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{37}N_4O_8$ 557.2606; found, 557.2618.

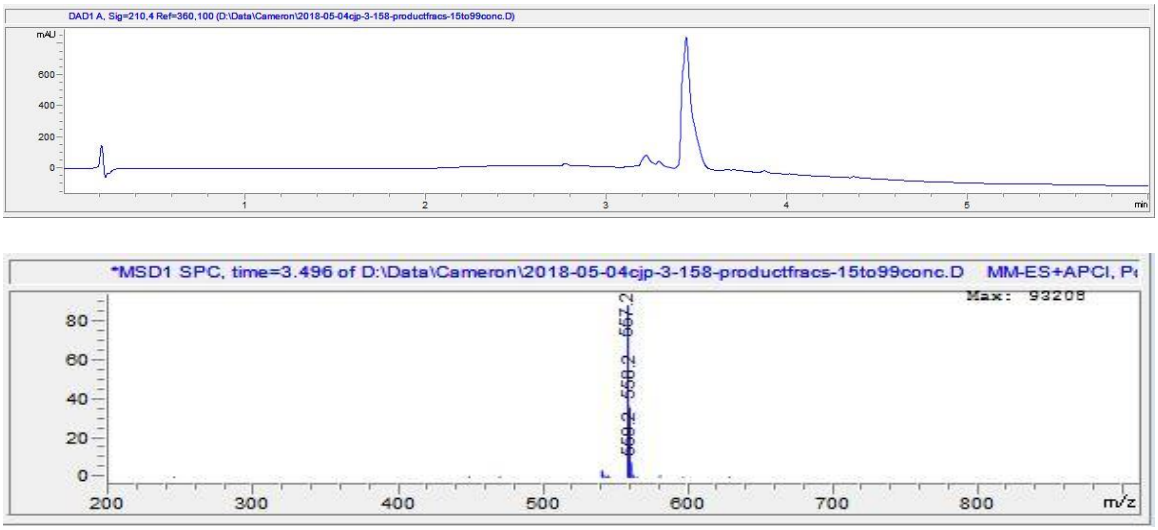
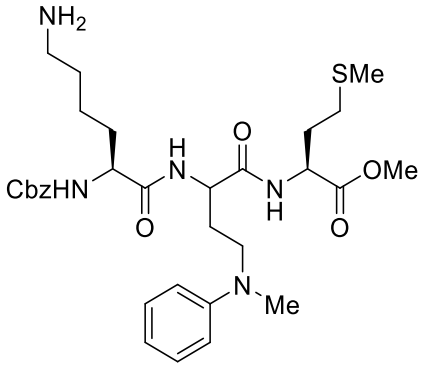


Figure S2.11. LCMS data for purified peptide **20**.



21: Cbz-Lys(Boc)-Dha-Met-OMe (30 mg, 0.05 mmol, 1 equiv) was treated with neat TFA (5 mL) and allowed to stir at room temperature until complete Boc deprotection was observed by LCMS. The

mixture was concentrated by rotary evaporation, diluted in MeCN (5 mL), and concentrated once more by rotary evaporation. The residue was carried forward as the TFA salt of Cbz-Lys-Dha-Met-OMe. Following the general procedure B, the reaction of Cbz-Lys-Dha-Met-OMe, N,N-dimethylaniline (30 μL, 0.25 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.5 mg, 0.0005 mmol, 0.01 equiv) provided an inseparable mixture of diastereomers of the product as the TFA salt (21 mg, 67% yield, 1.1:1 d.r. determined by NMR integral ratio of the bolded resonances below) as a white solid after purification by preparative HPLC (20 – 99% $MeCN/H_2O$, 0.1% TFA over 20 minutes).

For the mixture of diastereomers:

^{1}H NMR (600 MHz, MeOD) δ 7.55 – 7.46 (m, $4H_{dr1}$ + $4H_{dr2}$), 7.45 – 7.38 (m, $1H_{dr1}$ + $1H_{dr2}$), 7.35 – 7.30 (m, $4H_{dr1}$ + $4H_{dr2}$), 7.30 – 7.24 (m, $1H_{dr1}$ + $1H_{dr2}$), 5.11 – 5.03 (m, $2H_{dr1}$ + $2H_{dr2}$), 4.58 – 4.54 (m, $1H_{dr1}$ + $1H_{dr2}$), 4.49 – 4.40 (m, $1H_{dr1}$ + $1H_{dr2}$), **4.06 – 3.93 (m, $1H_{dr1}$ + $1H_{dr2}$)**, 3.75 – 3.56 (m, $5H_{dr1}$ + $5H_{dr2}$), 3.19 (s, $3H_{dr1}$ + $3H_{dr2}$), 2.92 – 2.85 (m, $2H_{dr1}$ + $2H_{dr2}$), 2.60 – 2.35 (m, $2H_{dr1}$ + $2H_{dr2}$), 2.14 – 1.96 (m, $6H_{dr1}$ + $6H_{dr2}$), 1.91 – 1.86 (m, $1H_{dr1}$ + $1H_{dr2}$), 1.82 – 1.59 (m, $4H_{dr1}$ + $4H_{dr2}$), 1.53 – 1.34 (m, $2H_{dr1}$ + $2H_{dr2}$).

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{31}H_{46}O_6N_5S$, 616.3163; found, 616.3164.

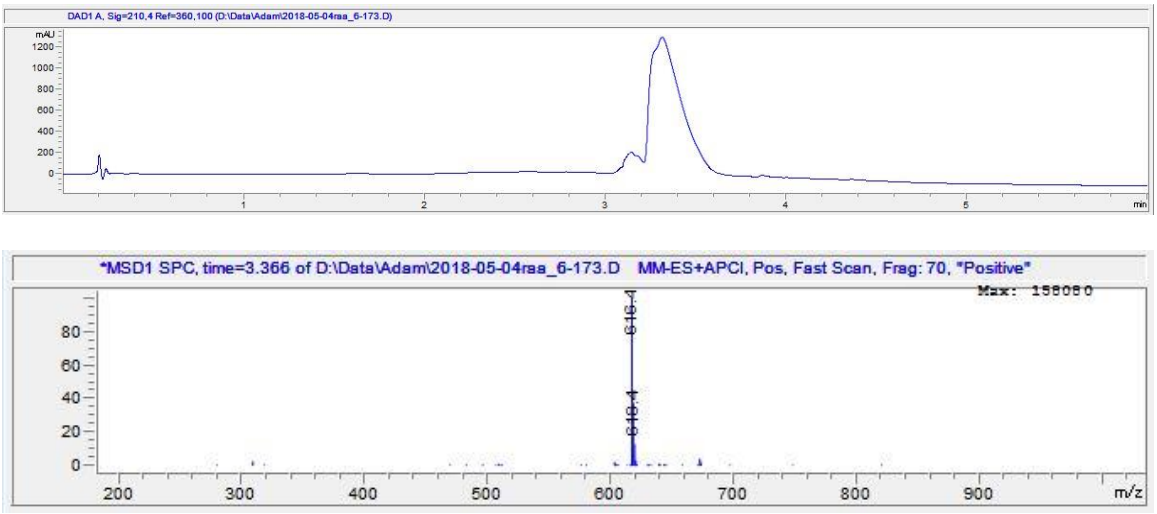
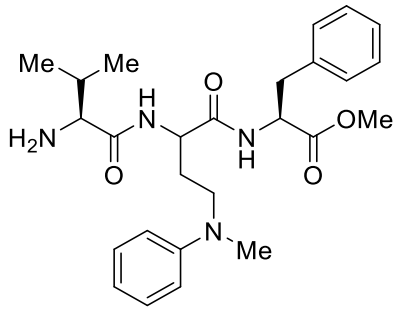


Figure S2.12. LCMS data for purified peptide **21**.



22: Boc-Val-Dha-Phe-OMe (25 mg, 0.01 mmol, 1 equiv) was treated with neat TFA (5 mL) and allowed to stir at room temperature until complete Boc deprotection was observed by LCMS. The mixture was concentrated by rotary evaporation, diluted in MeCN (5 mL), and concentrated once more by rotary evaporation. The residue was carried forward as the TFA salt of Val-Dha-Phe-OMe. Following the general procedure B, the reaction of Val-Dha-Phe-OMe, N,N-dimethylaniline (6.1 μL, 0.05 mmol, 5 equiv), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.5 mg, 0.0005 mmol, 0.01 equiv) provided two diastereomers of the prduct (Major: 17 mg, 49% yield, Minor: 4.0 mg, 12 % yield, 4:1 dr) as the TFA salt, a white solid, after purification by preparative HPLC (20 – 99% MeCN/H_2O, 0.1% TFA over 20 minutes).

Major Diastereomer:

^{1}H NMR (600 MHz, MeOD) δ 7.32 – 7.27 (m, 2H), 7.17 – 7.08 (m, 5H), 6.92 (dd, J = 10.7, 7.8 Hz, 3H), 4.70 (dd, J = 10.1, 5.1 Hz, 1H), 4.39 (dd, J = 8.8, 5.2 Hz, 1H), 3.69 (s, 3H), 3.64 (d, J = 5.9 Hz, 1H), 3.25 – 3.15 (m, 3H), 2.92 – 2.85 (m, 4H), 2.15 (dq, J = 13.5, 6.8 Hz, 1H), 1.72 (dtd, J = 13.5, 8.1, 7.6, 5.3 Hz, 1H), 1.63 – 1.55 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{37}O_4N_4$, 469.2810; found, 469.2813.

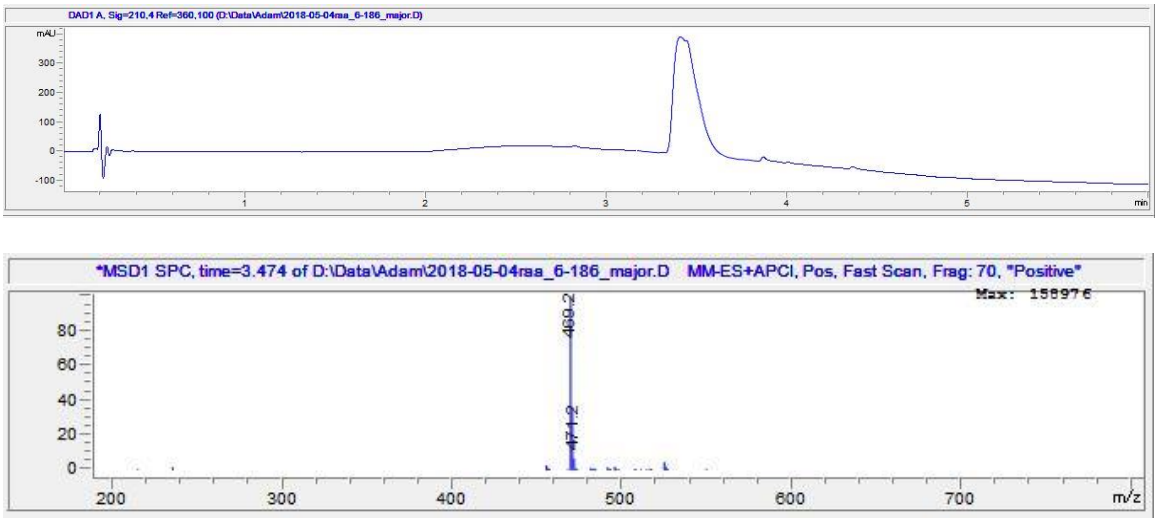


Figure S2.13. LCMS data for purified peptide **22** major diastereomer.

Minor Diastereomer:

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.40 – 7.33 (m, 2H), 7.23 (t, J = 7.5 Hz, 2H), 7.19 – 7.11 (m, 5H), 7.05 (t, J = 7.4 Hz, 1H), 4.65 (dd, J = 8.9, 5.4 Hz, 1H), 4.47 (t, J = 6.9 Hz, 1H), 3.67 (s, 3H), 3.63 (d, J = 5.8 Hz, 1H), 3.52 (tq, J = 13.8, 6.9, 5.9 Hz, 2H), 3.15 (dd, J = 14.0, 5.4 Hz, 1H), 3.06 (s, 3H),

2.96 (dd, J = 14.1, 8.9 Hz, 1H), 2.09 (dq, J = 13.6, 6.8 Hz, 1H), 1.97 (ddt, J = 12.6, 10.2, 6.3 Hz, 1H), 1.88 – 1.79 (m, 1H), 0.94 (d, J = 3.6 Hz, 3H), 0.93 (d, J = 3.5 Hz, 3H).

HRMS (NSI) m/z: $[M+H]^+$ calcd. for $C_{26}H_{37}O_4N_4$, 469.2809; found, 469.2812.

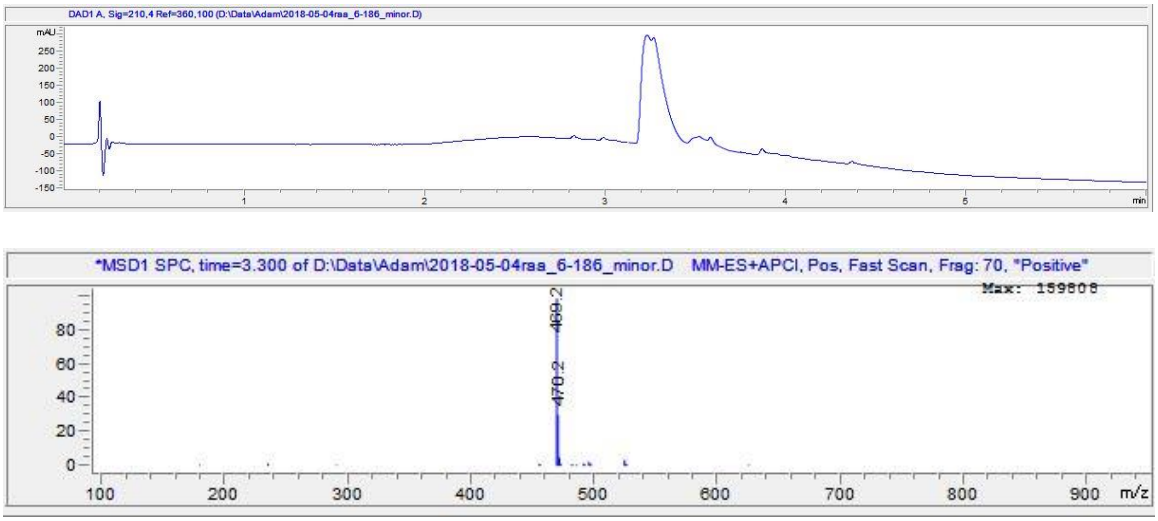
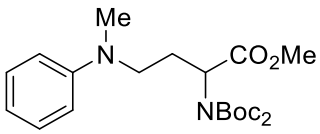


Figure S2.14. LCMS data for purified peptide **22** minor diastereomer.

2.4.5 Deprotection Procedure and Characterization Data



Methyl 2-(di(tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate: A screw-top test tube equipped with a stir bar was charged with $Ir(dF(CF_3)ppy)_2(dtbbpy)(PF_6)$ (3.6mg, 1 mol%) and methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate (91.5 mg, 0.3 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with acetonitrile (3 mL) and *N*,*N*-dimethylaniline (115 µL, 0.9 mmol, 3 equiv) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for

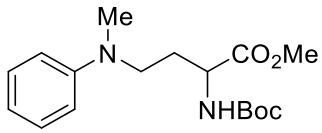
12 hours. The residue was purified by flash column chromatography (5 – 15% EtOAc/Hexanes) to afford the product (100 mg, 79%) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (t, J = 8.0 Hz, 2H), 6.72 (d, J = 8.2 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 4.91 (dd, J = 8.2, 6.0 Hz, 1H), 3.73 (s, 3H), 3.48 – 3.36 (m, 2H), 2.93 (s, 3H), 2.49 – 2.40 (m, 1H), 2.13 – 2.03 (m, 1H), 1.50 (s, 18H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 152.0, 149.1, 129.2, 116.4, 112.4, 83.3, 56.2, 52.3, 50.0, 38.3, 28.0, 27.3.

FTIR (neat) ν_{max}: 2974, 1753, 1735, 1710, 1600, 1504, 1032, 998, 847, 818, 794, 782, 757, 692, and 607 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{34}O_6N_2Na$, 445.2309; found, 445.2317.



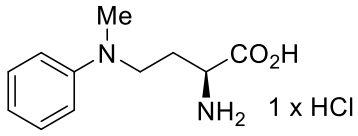
Methyl 2-((tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate: To a stirring soloution of methyl 2-(di(tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate (13 mg, 0.03 mmol, 1 equiv) in dichloromethane (9.8 mL) was added trifluoroacetic acid (0.2 mL) dropwise. The reaction was stirred 10 minutes and then concentrated by rotary evaporation. The residue was purified by flash column chromatography (10 – 20% EtOAc/Hexanes) to afford the product (5 mg, 54%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (dd, J = 8.8, 7.3 Hz, 2H), 6.78 – 6.66 (m, 3H), 5.15 (d, J = 7.9 Hz, 1H), 4.35 (q, J = 7.5 Hz, 1H), 3.68 (s, 3H), 3.46 – 3.35 (m, 2H), 2.90 (s, 3H), 2.13 (dq, J = 13.8, 6.0 Hz, 1H), 1.90 (dq, J = 14.3, 7.9 Hz, 1H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 155.4, 149.0, 129.2, 116.8, 112.6, 80.1, 52.3, 51.8, 49.3, 38.7, 29.7, 28.3.

FTIR (neat) ν_{max}: 3341, 2976, 1745, 1712, 1642, 1601, 1507, 1336, 1162, 1051, 990, 868, 749, 689, and 659 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{27}O_4N_2$, 323.1963; found, 373.1963.



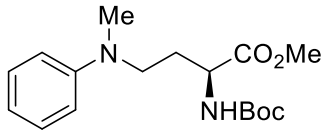
(*S*)-2-amino-4-(methyl(phenyl)amino)butanoic acid hydrochloride: To a round bottom flask equipped with a stir bar was added (+)/(-)benzyl-2-(tert-butyl)-4-(2-(methyl(phenyl)amino)ethyl)-5-oxooxazolidine-3-carboxylate (75.8 mg, 0.19 mmol, 1 equiv) and concentrated aqueous HCl (2 mL). The reaction was stirred at 80 °C for 30 minutes then concentrated by rotary evaporation to afford the product (39.1 mg, 99%) as a white solid.

^{1}H NMR (600 MHz, D_2O) δ 7.62 – 7.46 (m, 5H), 3.98 (dd, J = 7.8, 5.2 Hz, 1H), 3.88 – 3.72 (m, 2H), 3.26 (s, 3H), 2.21 – 1.98 (m, 2H).

^{13}C NMR (151 MHz, D_2O) δ 170.9, 139.3, 130.9, 130.8, 121.0, 55.4, 50.5, 45.5, 25.5.

FTIR (neat) ν_{max}: 2826, 2508, 1737, 1730, 1573, 1487, 1203, 1127, 1078, 765, 616, and 551 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{16}O_2N_2Cl$, 243.0895; found, 243.0903.



Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate: To a round bottom flask equipped with a stirbar was added 2-amino-4-(methyl(phenyl)amino)butanoic acid dihydrochloride (39 mg, 0.19 mmol, 1 equiv) and a ether/methanol solution (1:1, 10 mL). The reaction was placed under a nitrogen atmosphere and cooled to 0 °C. (Trimethylsilyl)diazomethane solution

(2.0 M in diethyl ether, 0.20 mL, 0.40 mmol, 2 equiv) was added dropwise via syringe and the reaction was warmed to room temperature and stirred for 10 minutes. The reaction was quenched with acetic acid (2 mL) and then concentrated by rotary evaporation. The residue was transferred to another round bottom flask equipped with a stirbar and was dissolved in an acetonitrile/water solution (3:1, 12ml). To this stirring solution, di-tert-butyl decarbonate (0.13 ml, 0.56 mmol, 3 equiv), 4-dimethylaminopyridine (5 mg, 0.038 mmol, 0.2 equiv), and sodium bicarbonate (33 mg, 0.38 mmol, 2.1 equiv) were added and allowed to stir until HPLC indicated the starting material had been consumed. The reaction was concentrated to remove acetonitrile and then diluted with water (2 mL). The aqueous solution was extracted with EtOAc (3 x 2 mL), and the combined extracts were concentrated by rotary evaporation. The residue was purified by flash column chromatography (10 – 20% EtOAc/Hexanes) to afford the product as a colorless oil. Chiral HPLC analysis (OD-H, 10% IPA/hexanes, 1.0 mL/min, 254 nm) indicated 96% ee for the major enantiomer (tR (major) = 11.833 min, tR (minor) = 9.180 min). The physical properties and spectral data match the values of the racemate reported herein.

2.5 Chapter Two References

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Chapter 3:

Radical α-C–H Cyclobutylation of Aniline Derivatives

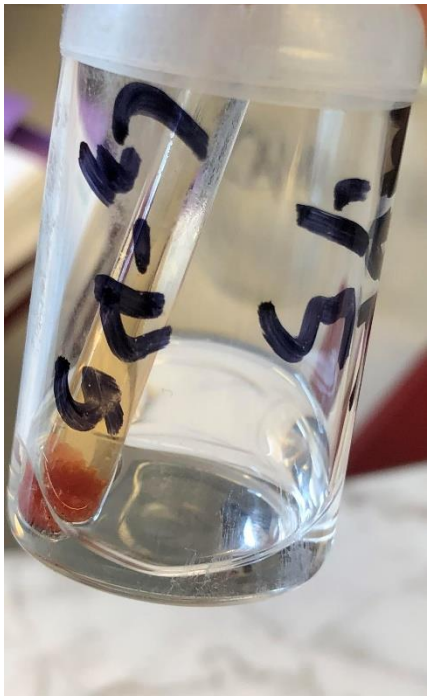


Figure 3.1 Key recrystallization setup used to identify major isomer of cyclobutylation process.

Reprinted and adapted with permission from (**C. J. Pratt**, R. A. Aycock, M. D. King, and N. T. Jui Radical α-C–H Cyclobutylation of Aniline Derivatives. Synlett. 2019, 31,51–54.)

(M. D. King, undergraduate mentee, prepared starting materials for this project)

3.1 Introduction

With a focus of finding new partners for the alpha amino radical, our research took a turn into the world of strained-ring systems. Here we attempted to add this radical to a C-C bond. Typically, C-C single bonds are poor partners for radicals to add into (in comparison to C=C double bonds as seen in chapter 2) and would appear to be an unfit partner. This is of course because C-C bonds are known to be stable and chemically inert. However, conformationally strained-ring systems display reactivity profiles similar to olefins and allow for addition to occur. Indeed, early work by Wiberg and co-workers and by Gaoni demonstrated that many strained polycyclic hydrocarbons (some of which are shown in Figure 3.2) can be synthesized,[70-72] and used as effective alkylating agents.[73,74] We synthesized a range of the strain-release reagents and began to investigate if they could operate as partners different radicals formed under photochemical conditions. Preliminary studies done by the author showed

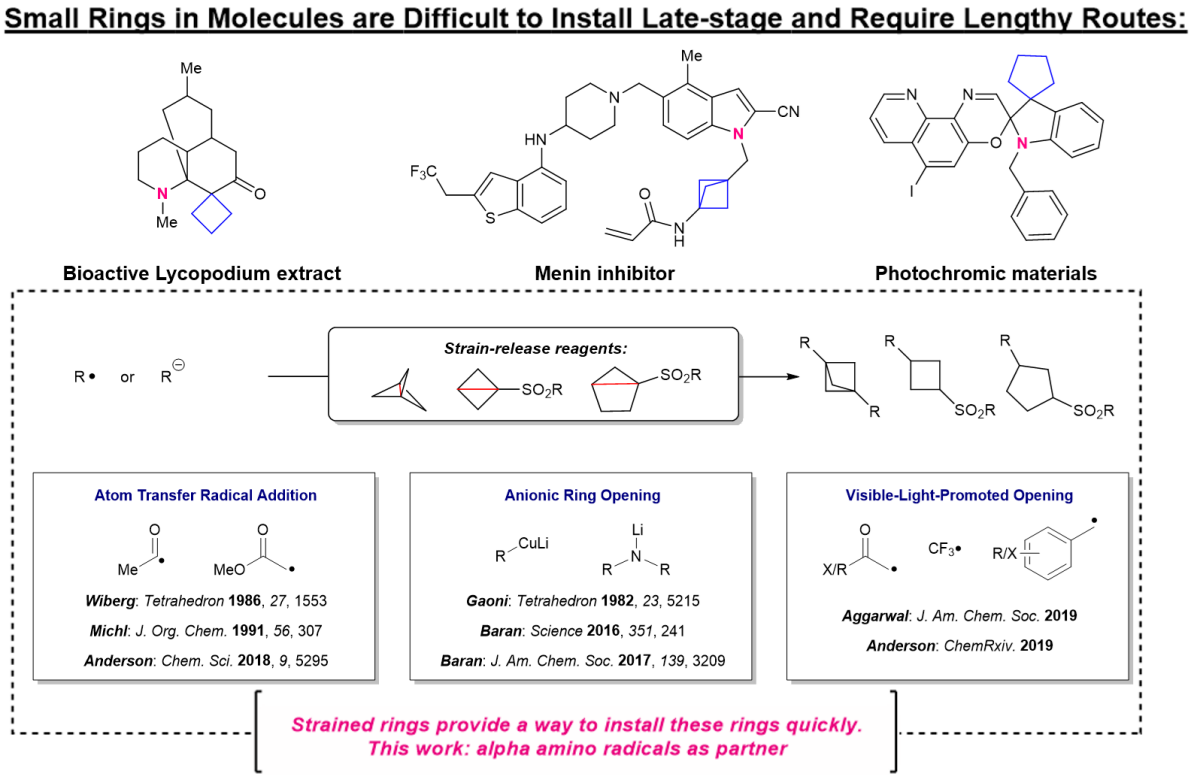


Figure 3.2 A strained approach to small ring installation.

success with addition to bicyclo[1.1.0]butane (BCB) derivatives by the alpha amino radical (albeit at low yields).

In addition to anionic nucleophiles,[75-77] organometallics,[78-80] and amines[81,82] strained BCBs have already been shown to be effective coupling partners for radical species.[77,83] When a radical or anion adds to BCB, the strained ring breaks open revealing a cyclobutane unit. This meant that as a partner in our system, BCB could furnish amines that would be cyclobutylated at the alpha position (assuming a similar mechanism to the one outlined in chapter 2). We hoped this process would be similarly highly selective and would again not require stoichiometric additives. It had become clear that this could become a potentially valuable method for the synthesis of cyclobutane-containing natural products or lead drug candidates. Although a number of methods for cyclobutylation of radical intermediates have been already disclosed (most recently by the groups of Lin[84] and Aggarwal[85]) this approach would be unique thanks to its ability to work on nonactivated amines. We again chose to not use pre-functionalized amines to sidestep the need for specialized amine synthesis.

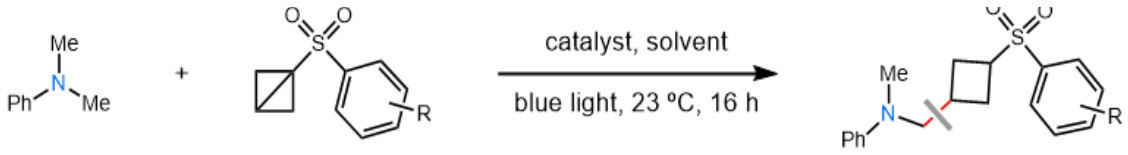
A similar catalytic pathway was expected to operate as seen in chapter 2. We assumed that an oxidizing photocatalyst could remove an electron from the amine substrate and give rise to a radical cation. Deprotonation of the C-H bond alpha to the nitrogen would provide the aforementioned α -amino radical species.[20,21,25,29,86-93] Addition of this species to the strained BCB ring would afford a new C-C bond at the cost of the strained C-C bond. Finally, single electron reduction and protonation would close the catalytic cycle and provide the desired cyclobutylamine.

3.2 Results and Discussion

At first, we found the proposed transformation was difficult to achieve in high yields. As shown in Table 3.1, treatment of *N,N*-dimethylaniline (DMA) with the BCB reagent from entry 1 gave only a 28% yield. Tweaking of the catalyst, solvent, and amine loading provided no significant gains in the yield. We then turned our attention to the BCB reagent itself and synthesized a small series

of BCB reagents that contained electron withdrawing groups on the aryl group. We believed that in order to make this C-C bond act more like an electron poor C=C bond, we would need these types of groups. As seen in entry 2 and 3, the yield was more then doubled. Specifically, the 4-CF_3 and 3,5-diF ring additions gave the desired product in 64 and 69% respectively. Taking what we had learned from our peptide functionalization system, we also used high amine loadings (5 equivalents) to prevent further activation and cyclobutylation of the desired products. We found this reaction did not operate in the absence of a photoredox catalysis of light (as would be expected if this is a photoredox driven method). Other non-metal containing catalysts could also be employed to accomplish this transformation, although were less efficient across a range of substrates. Entry 3-6 showcase how once again a variety of aprotic organic solvents could be utilized here with acceptable levels of reaction efficiency (entries 46–69% yield).

Table 3.1 Optimal Conditions for alpha-Cyclobutylation of DMA



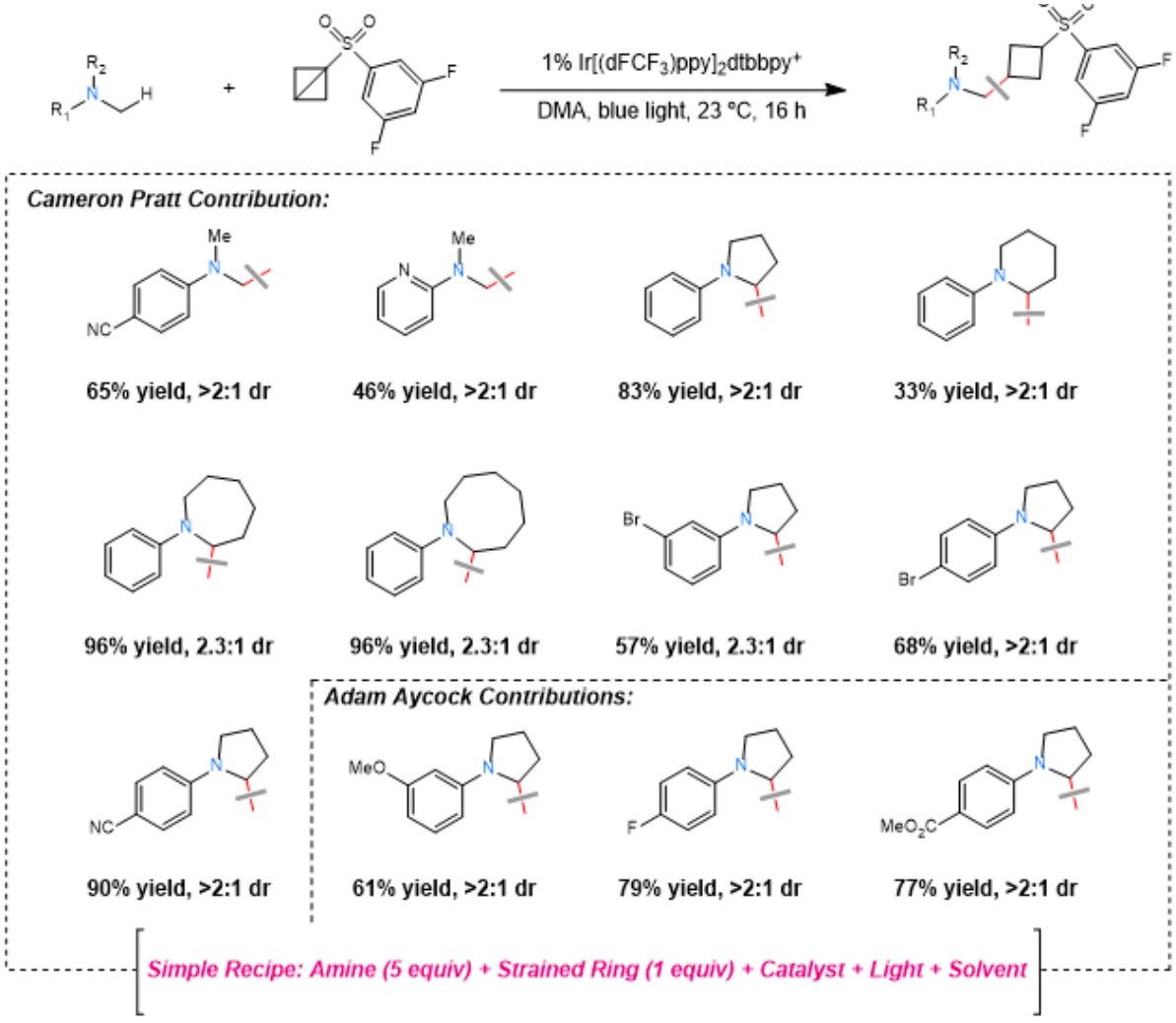
Entry	*Solvent*	*Aryl R-Group*	*% yield A*
1	DMA	**H**	**28%**
2	DMA	**4-CF_3**	**64%**
3	DMA	**3,5-diF**	**69%**
4	MeCN	3,5-diF	48%
5	DCE	3,5-diF	46%
6	DMSO	3,5-diF	51%

Key Finding: Bicyclobutane Partner Needs to be Electron Poor

Having solved the problem of early low yields in this project, we began to explore the substrate scope of this protocol. As shown in Table 3.2, both the cyanoarene and hetero-atom containing DMA

reacted under the optimal conditions to produce the desired products in yields of 65 and 46% respectively. Cyclic aniline derivatives were also largely found to be particularly effective under these conditions. The 5-member ring *N*-phenylpyrrolidine reacted to give an impressive 83% isolated yield. Surprisingly, these conditions were less effective for the coupling of *N*-phenylpiperidine (the 6-membered ring) and only gave 33% yield. The remaining yield was starting material in this case (no significant product activation was observed). We believe this was in part due to the increased steric constraints presented by the ordered chair-like system. Efficient reactivity returned upon the use of seven- and eight-membered saturated nitrogen heterocycles, giving rise to the corresponding cyclobutane containing products in near-quantitative yield (96% in each case). In accord with earlier

Table 3.2 Scope of anilines for method.



reports and our own previous work, aniline derivatives with electron-donating groups in the ortho- or para-positions were not reactive. Here, coupling attempts returned the starting materials unchanged. We next took the *N*-phenylpyrrolidine and explored various functionality appended to the ring. Bromine was shown to be tolerated in multiple ring positions giving a 57% yield from the meta-position and 68% yield from the para-position. As expected, the cyanoarene containing *N*-phenylpyrrolidine was highly efficient providing a 90% yield. Adam Aycock also showed that a methoxy substituent moved to the meta-position in *N*-phenylpyrrolidine was well tolerated and provided a 61% yield. Finally, he showcased how the para-position could handle a fluorine substituent and ester group at 79% and 77% respectively. A range of more complex amines were also attempted with little success. Although coupling was observed, it was in low yields. It appeared the steric environment of the amine in relation to the BCB reagent was a tricky balance to strike.

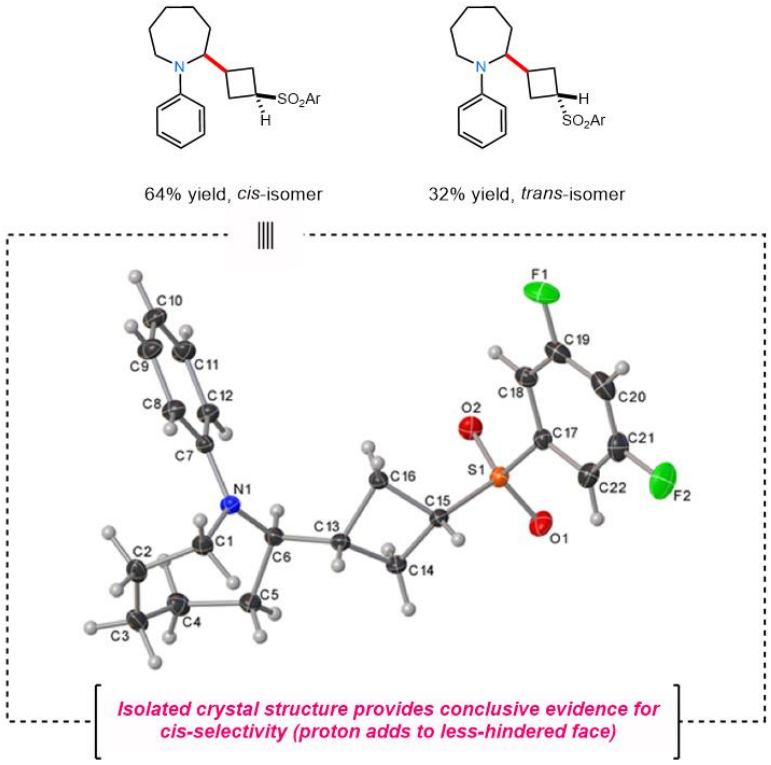
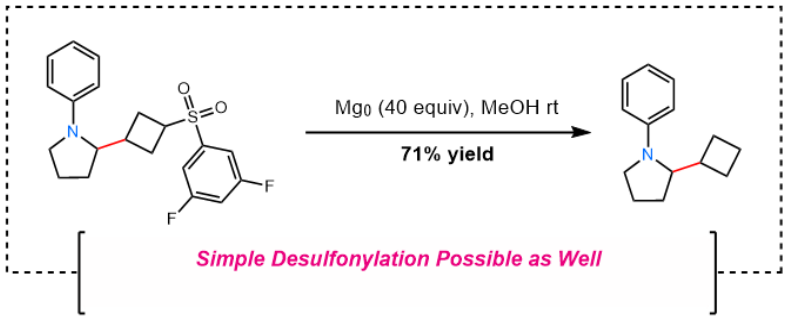


Figure 3.3 Determination of the stereoisomers was confirmed using X-ray crystallography.

Isolation of the products in the scope typically resulted in both *cis*- and *trans*-cyclobutane stereoisomers being isolated at roughly 1:1 dr. In some cases, higher selectively was also observed. In these cases, we suspected that the isomer forming in excess was the *cis*-isomer. We believed that in line with our previous work, the protonation was likely occurring at the less hindered face. Although separation of these isomers was often difficult, we were able to purify the major isomer of the seven-membered saturated nitrogen heterocycle. After developing both patience and the correct crystallization conditions, the isomer permitted its analysis by X-ray crystallography. Our theory was proven correct and the cis-cyclobutane product was indeed observed!

Finally, we showed that removal of the sulfur containing handle was possible under mild conditions (as shown in Scheme 3.1). This maneuver was in line with previous reports and reductive desulfonylation of the *N*-phenylpyrrolidine product occurred quickly in the presence of excess magnesium in methanol at room temperature to give a 71% yield. However, if the handle is retained it can be leveraged for its synthetic utility. This has been extensively documented by the Baran group.[82]



Scheme 3.1 Reductive desulfonation of arylsulfonylcyclobutane

3.3 Conclusion

This project showcases how the alpha amino radical formed from a range of anilines can be applied to strained rings. This new partner allowed for the development of a simple and mild method that engaged direct C–H cyclobutylation of aniline derivates. A key factor in this system was utilizing particularly electron poor strained ring systems. Once this was discovered, many *N*-aryl amines and heterocyclic compounds of various ring sizes were shown to be effective radical precursors that

required no previous functionalization. In accord with previous reports and our own work, electron-deficient aniline derivates were the most efficient coupling partners. We believe that because the resulting sulfonyl cyclobutane products can be manipulated in several ways, we anticipate this process will be an attractive method for the generation of a range of α-cyclobutyl amine derivatives.

3.4 Supporting Information

3.4.1 General Information

All reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (PARsource PowerPAR LED Bulb-Blue 15 Watt/440 nm, available at www.1000bulbs.com). Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Anilines, sulfonyl chlorides, 4-bromobut-1-ene, Oxone, L-proline, CuI, and secondary amines were purchased from Aldrich Chemical Co., Alfa Aesar, Combi Blocks, or Oakwood Products and were used as received. Photoredox catalysts, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, $[Ir(ppy)_2(dtbbpy)]PF_6$, 5CzBN, 4CzIPN, and 3DPAFIPN were prepared according to literature procedures.[11,12,67] DMSO, DMF, and MeCN were purified on a Pure Process Technologies solvent purification system. Reaction solvents were degassed in a sidearm flask by applying vacuum and backfilling with N_2 (this process was conducted a total of three times) while subject to sonication.

All yields refer to isolated yields. New compounds were characterized by proton, carbon, and fluorine NMR spectroscopy. NMR data were recorded on one of three spectrometers: Bruker 600 MHz, INOVA 600 MHz, INOVA 500 MHz and INOVA 400 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR). Adduct yields for comparison of bicyclobutane (BCB) reagents (**1a-1c**) were obtained via ^{1}H NMR with an INOVA 600 MHz NMR using 1,3-benzodioxole as the internal standard. Adduct yields for further optimization of **1c** were obtained via ^{19}F NMR with an INOVA 400 MHz NMR using fluorobenzene as the internal standard.

3.4.2 General Procedures

Procedure for Radical Conjugate Addition: A screw-top test tube equipped with a stir bar was charged with Ir[dF(CF3)ppy]2(dtbbpy)PF6 PF_6 (1 mol%), 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (1 equiv), and aniline if solid (5 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with previously degassed solvent (DMA, 2 mL/mmol 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane) and aniline if liquid (5 equiv) by syringe. The resulting suspension was stirred under irradiation with blue LEDs (4 cm from lamp) for 16 hours at a stirring speed of 700 rpm. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with 5% LiCl (3 x 15 ml), brine (2 x 15 ml), dried with Na_2SO_4, evaporated in vacuo, and purified by silica gel to give the cyclobutylsulfone products.

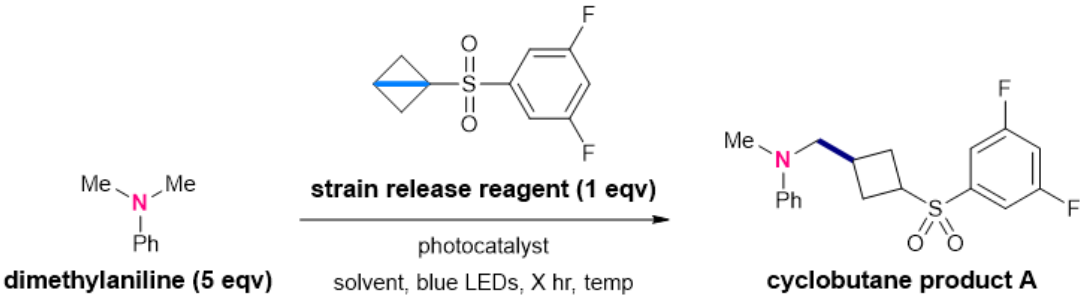
Procedure for Removal of Arylsulfone Handle: The α-cyclobutyl aniline product was dissolved in MeOH (0.04 M) and refluxed with freshly activated Mg turnings (40 eqv). After completion of the reaction (2 hours), the mixture was cooled to room temperature, diluted with EtOAc, washed with sat. aq. NH_4Cl and brine, dried with Na_2SO_4, evaporated in vacuo, and purified by silica gel flash chromatography to afford the title compound.

3.4.3 Optimization Details

Optimization Procedure: A screw-top test tube equipped with a stir bar was charged with or without photoredox catalyst (1-5 mol%) and 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (23 mg, 0.1 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a vacuum line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). Under N_2 atmosphere, the tube was charged with previously

degassed solvent (200 μl) and dimethylaniline (63 μl, 0.5 mmol, 5 equiv) by syringe. The resulting suspension was stirred under irradiation with or without blue LEDs (4 cm from lamp) for 16-24 hours at room temperature, 50 °C or 80 °C. Upon completion, an internal standard of fluorobenzene (9.4 μl, 0.1 mmol, 1 equiv) was delivered to the test tube and the contents were thoroughly mixed in $CDCl_3$. An aliquot was analyzed by ^{19}F NMR and the integral values were used to calculate yield.

Table S3.1. The influence of solvent, catalyst, heating, and time on yield of cyclobutane product A



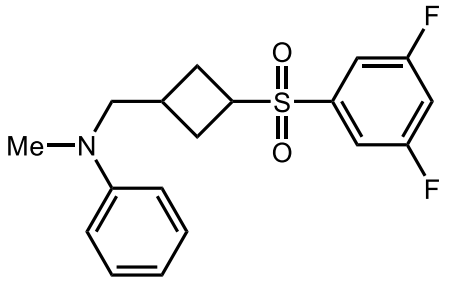
Catalyst	Solvent	Heating	Time	% Yield A[1]
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMF	no heating	16 hr	63%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DCM	no heating	16 hr	27%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	Toluene	no heating	16 hr	42%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DCE	no heating	16 hr	46%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN	no heating	16 hr	48%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMSO	no heating	16 hr	51%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	no heating	16 hr	69%
$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA	no heating	16 hr	35%
5CzBn (5%)	DMA	no heating	16 hr	64%
4CzIPN	DMA	no heating	16 hr	56%
3DPAFIPN	DMA	no heating	16 hr	26%
EOSIN Y	DMA	no heating	16 hr	14%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	heat to 50 °C	16 hr	57%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	heat to 80 °C	16 hr	53%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	no heating	24 hr	67%
none	DMA	no heating	16 hr	0%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$[2]	DMA	no heating	16 hr	0%

[1]Yield determined via fluorine NMR using fluorobenzene as internal standard. [2]Reaction ran without blue LEDs.

3.4.4 Preparation of Starting Materials

1-Phenylpyrrolidine, 1-phenylpiperidine, 1-phenylazepane, 1-phenylazocane, substituted phenylpyrrolidines, and BCB reagents (**1a-1c**) were prepared according to literature procedures.[82,94-98]

3.4.5 Procedure and Characterization Data



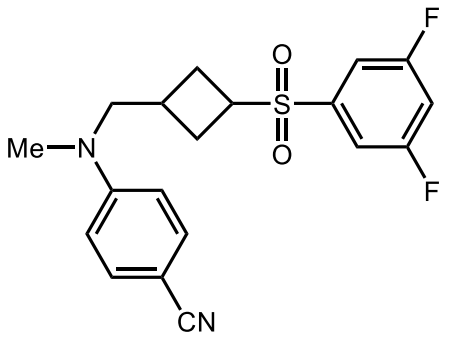
***N*-((3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)methyl)-*N*-methylaniline, 2c:** Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (114.4 mg, 0.5 mmol, 1 equiv), dimethylaniline (320 μl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5.8 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (151 mg, 57% yield, 5:6 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear oil after purification by flash column chromatography (25% ethyl acetate:hexanes to 40% ethyl acetate:hexanes).

For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 13.6, 3.9 Hz, , $2H_a$ + $2H_b$), 7.21 (dd, *J* = 15.1, 7.2 Hz, $2H_a$ + $2H_b$), 7.08 (t, *J* = 8.4 Hz, $1H_a$ + $1H_b$), 6.72 – 6.66 (m, $3H_a$ + $3H_b$), **3.78 (ttd, *J* = 9.0, 6.0, 1.1 Hz, $1H_a$), 3.66 (p, *J* = 8.6 Hz, $1H_b$)**, 3.41 (d, *J* = 6.8 Hz, $2H_b$), 3.36 (d, *J* = 7.3 Hz, $2H_a$), 2.93 (s, $3H_b$), 2.90 (s, $3H_a$), 2.67 – 2.60 (m, $2H_a$ + $2H_b$), 2.35 – 2.25 (m, $2H_a$ + $2H_b$), 2.14 – 2.06 (m, $1H_a$ + $1H_b$).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.8 (dd, *J* = 11.3, 2.5 Hz), 162.1 (dd, *J* = 11.3, 2.6 Hz), 149.6 , 149.1 , 141.5 (dt, *J* = 21.6, 7.9 Hz), 129.3 , 129.2 , 117.0 , 116.8 , 112.7 , 112.5 , 111.8 (ddd, *J* = 21.6, 19.3, 6.4 Hz), 109.4 (t, *J* = 24.9 Hz), 57.4 , 57.2 , 54.8 , 53.6 , 39.2 , 39.0 , 29.7 , 28.3 , 27.5 , 26.4 , 22.8 , 16.9 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.85 (dd, *J* = 8.0, 5.6 Hz), -104.91 (dd, *J* = 8.6, 5.0 Hz).



4-(((3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)methyl)(methyl)amino)benzonitrile, 3: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115.6 mg, 0.5 mmol, 1 equiv), 4-(Dimethylamino)benzonitrile (367 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF$_6$ (6.0 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (123 mg, 65% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear oil after purification by flash column chromatography (40% ethyl acetate:hexanes).

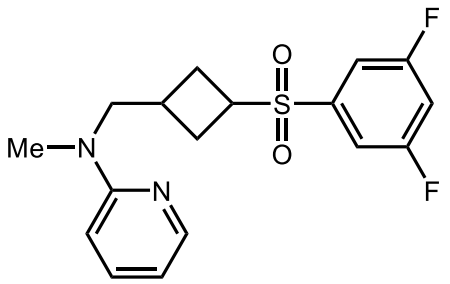
For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.39 (dd, *J* = 8.7, 6.5 Hz, 2H$_a$ + 2H$_b$), 7.36 – 7.30 (m, 2H$_a$ + 2H$_b$), 7.03 (tt, *J* = 8.7, 2.5 Hz, 1H$_a$ + 1H$_b$), 6.56 (td, *J* = 6.6, 1.4 Hz, 2H$_a$ + 2H$_b$), **3.72 (ddd, *J* = 14.8, 9.4, 5.6 Hz, 1H$_a$), 3.63 (p, *J* = 8.5 Hz, 1H$_b$)**, 3.45 (d, *J* = 6.9 Hz, 2H$_b$), 3.39 (d, *J* = 7.4 Hz, 2H$_a$),

2.97 (d, *J* = 0.8 Hz, $3H_b$), 2.94 (s, $3H_a$), 2.91 (m, $1H_a$) 2.63 – 2.57 (m, $1H_a$ + $2H_b$), 2.27 (t, *J* = 8.5 Hz, $2H_a$ + $2H_b$), 2.05 (ddd, *J* = 14.6, 9.0, 6.5 Hz, $1H_a$ + $1H_b$).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.8 (d, *J* = 11.5 Hz), 162.1 (d, *J* = 11.4 Hz), 151.6 , 151.4 , 141.3 (t, *J* = 7.6 Hz), 141.1 (t, *J* = 8.0 Hz), 133.6 , 120.4 , 120.4 , 111.8 (ddd, *J* = 26.0, 21.7, 6.6 Hz), 111.5 , 111.5 , 109.6 (t, *J* = 25.0 Hz), 98.1 , 98.0 , 56.4 , 56.3 , 54.6 , 53.3 , 39.2 , 39.0 , 29.7 , 28.1 , 27.1 , 26.4 .

^{19}F NMR (376 MHz, Chloroform-d) δ -104.58 – -104.61 (m), -104.66 – -104.69 (m).



4-(((3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)methyl)(methyl)amino)benzonitrile, 4: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116.1 mg, 0.5 mmol, 1 equiv), 2-(dimethylamino)pyridine (310 μl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (6.0 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (123 mg, 46% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear oil after purification by flash column chromatography (30% ethyl acetate:hexanes).

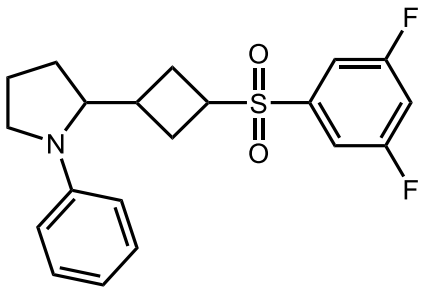
For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ **8.06 (dd, *J* = 5.1, 1.9 Hz, 1Ha), 8.02 (dd, *J* = 5.1, 1.9 Hz, 1 Hb)**, 7.41 – 7.30 (m, $3H_a$ + $3H_b$), 7.01 (tdt, *J* = 8.4, 4.0, 2.4 Hz, $1H_a$ + $1H_b$), 6.53 – 6.44 (m, $1H_a$ + $1H_b$), 6.39 (dd, *J* = 17.1, 8.6 Hz, $1H_a$ + $1H_b$), 3.83 – 3.53 (m, $3H_a$ + $3H_b$), 2.98 (s, $3H_a$), 2.90 (s, $3H_b$),

2.83 (h, J = 7.6, 6.9 Hz, 1H_b), 2.64 – 2.50 (m, 2H_a + 1H_b), 2.33 – 2.20 (m, 2H_a + 2H_b), 2.08 (td, J = 11.4, 9.2, 6.0 Hz, 1H_a + 1H_b).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.7 (d, J = 11.4 Hz), 162.0 (d, J = 11.3 Hz), 158.2 , 147.6 , 141.5 (t, J = 6.1 Hz), 137.4 , 112.3 – 111.4 (m), 109.3 (td, J = 24.9, 6.5 Hz), 105.7 , 105.5 , 54.8 , 54.6 , 53.6 , 37.6 , 36.6 , 29.7 , 28.9 , 27.5 , 26.1 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.94 (dd, J = 8.2, 5.0 Hz), -105.06 (t, J = 6.8 Hz).



2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpyrrolidine, 5: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115.6 mg, 0.5 mmol, 1 equiv), 1-phenylpyrrolidine (360 µl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5.8 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (157 mg, 83% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (30% ethyl acetate:hexanes).

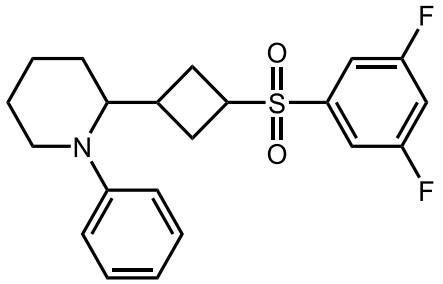
For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.47 – 7.33 (m, 2H_a + 2H_b), 7.25 – 7.19 (m, 2H_a + 2H_b), 7.12 – 7.04 (m, 1H_a + 1H_b), 6.72 – 6.59 (m, 3H_a + 3H_b), **3.91 (t, J = 6.1 Hz, 1H_a), 3.86 (q, J = 5.2 Hz, 1H_b)**, 3.67 (tt, J = 8.3, 4.1 Hz, 1H_a), 3.64 – 3.51 (m, 1H_a + 1H_b), 3.52 – 3.44 (m, 1H_b), 3.14 (dt, J = 16.4, 8.7 Hz, 1H_a + 1H_b), 2.99 (dq, J = 16.3, 8.7 Hz, 1H_a), 2.64 – 2.28 (m, 3H_a + 3H_b), 2.29 – 2.18

(m, $1H_a$ + $1H_b$), 2.14 (ddd, *J* = 11.5, 7.8, 4.4 Hz, $1H_b$), 2.04 – 1.88 (m, $4H_a$ + $4H_b$), 1.79 – 1.72 (m, $1H_a$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.9 (dd, *J* = 11.4, 5.3 Hz), 161.8 (dd, *J* = 11.4, 5.3 Hz), 148.7 , 148.0 , 141.4 (t, *J* = 7.9 Hz), 129.2 , 129.1 , 116.2 , 116.2 , 112.5 , 112.3 , 111.9 (dd, *J* = 11.5, 7.2 Hz), 111.8 (dd, *J* = 11.3, 7.3 Hz), 109.3 (td, *J* = 25.0, 3.4 Hz), 60.0 , 60.0 , 54.9 , 53.2 , 50.1 , 49.3 , 36.4 , 33.7 , 28.6 , 27.8 , 27.0 , 25.7 , 25.7 , 25.6 , 23.9 , 23.9.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.86 (dd, *J* = 8.6, 5.6 Hz), -104.92 (dd, *J* = 8.6, 5.4 Hz).



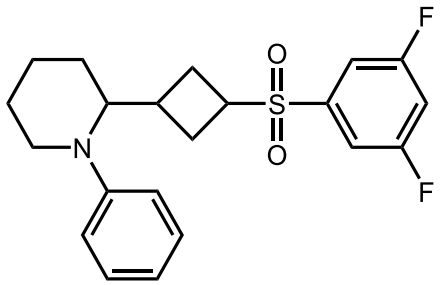
2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpiperidine, 6_a: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115.1 mg, 0.5 mmol, 1 equiv), 1-phenyl piperidine (400 μl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (6.5 mg, 0.005 mmol, 0.01 equiv) provided the product (37.6 mg, 19% yield) as a clear oil after purification by flash column chromatography (5% ethyl acetate:hexanes to 20% ethyl acetate:hexanes).

For the major isomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.26 – 7.22 (m, 2H), 7.18 – 7.12 (m, 1H), 6.99 (tt, *J* = 8.4, 2.3 Hz, 1H), 6.90 (d, *J* = 7.7 Hz, 2H), 6.77 (t, *J* = 6.9 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.44 (p, *J* = 8.6 Hz, 1H), 3.16 (dt, *J* = 12.7, 4.2 Hz, 1H), 2.90 (ddd, *J* = 13.2, 9.5, 4.3 Hz, 1H), 2.69 (dt, *J* = 18.0, 9.1 Hz, 1H), 2.12 (t, *J* = 9.4 Hz, 2H), 1.87 (dt, *J* = 12.1, 9.4 Hz, 1H), 1.67 (ddt, *J* = 9.2, 7.5, 5.9 Hz, 2H), 1.58 – 1.39 (m, 5H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.7 (d, *J* = 11.5 Hz), 162.0 (d, *J* = 11.2 Hz), 151.7 , 141.5 (t, *J* = 7.8 Hz), 129.1 , 119.9 , 118.2 , 112.4 – 111.2 (m), 109.2 (t, *J* = 24.9 Hz), 62.5 , 53.1 , 45.1 , 29.5 , 28.7 , 26.9 , 25.6 , 25.0 , 20.2 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.09 (dd, *J* = 8.4, 5.4 Hz).



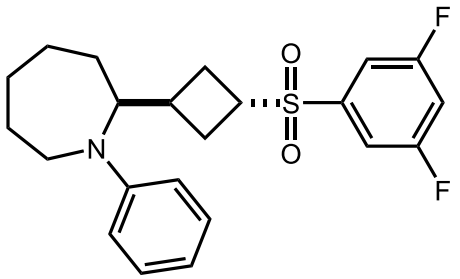
2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpiperidine, 6$_b$: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115.1 mg, 0.5 mmol, 1 equiv), 1-phenyl piperidine (400 µl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF$_6$ (6.5 mg, 0.005 mmol, 0.01 equiv) provided the product (25 mg, 13% yield) as a clear oil after purification by flash column chromatography (5% ethyl acetate:hexanes to 20% ethyl acetate:hexanes).

For the minor isomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 – 7.29 (m, 2H), 7.12 (t, *J* = 7.9 Hz, 2H), 7.00 (tt, *J* = 8.4, 2.3 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 3.66 (dt, *J* = 10.9, 3.8 Hz, 1H), 3.51 (tt, *J* = 9.4, 4.7 Hz, 1H), 3.25 (dd, *J* = 13.0, 3.2 Hz, 1H), 3.19 – 3.11 (m, 1H), 3.01 – 2.93 (m, 1H), 2.51 (ddt, *J* = 13.1, 8.3, 3.7 Hz, 1H), 2.17 (dq, *J* = 13.3, 4.7, 4.2 Hz, 1H), 1.95 (ddd, *J* = 16.8, 8.8, 4.9 Hz, 1H), 1.79 (dt, *J* = 13.5, 8.4 Hz, 1H), 1.63 (ddd, *J* = 15.3, 10.6, 4.8 Hz, 1H), 1.56 – 1.48 (m, 4H), 1.42 (dd, *J* = 12.8, 3.3 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.7 (d, *J* = 11.4 Hz), 161.0 (d, *J* = 11.4 Hz), 150.7 , 140.4 (t, *J* = 7.8 Hz), 128.1 , 117.8 , 116.1 , 110.8 (dd, *J* = 21.7, 6.4 Hz), 108.3 (t, *J* = 25.0 Hz), 60.8 , 53.5 , 43.0 , 29.2 (d, *J* = 168.7 Hz), 26.0 , 25.5 , 24.0 , 23.6 , 18.7 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.07 (dt, *J* = 9.0, 4.9 Hz).

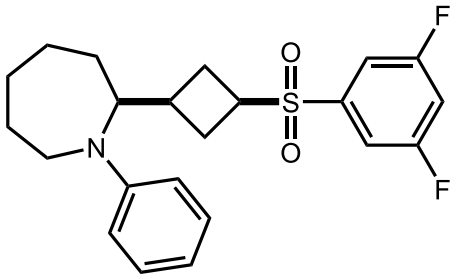


2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazepane, 7*$_{trans}$*: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116.6 mg, 0.5 mmol, 1 equiv), 1-phenyl piperidine (450 μl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF$_6$ (6.4 mg, 0.005 mmol, 0.01 equiv) provided the product (64 mg, 32% yield) as a clear oil after purification by flash column chromatography (0% ethyl acetate:hexanes to 20% ethyl acetate:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, 2H), 7.15 (t, *J* = 8.1 Hz, 1H), 7.04 (tt, *J* = 8.5, 2.1 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 2H), 6.57 (t, *J* = 7.2 Hz, 1H), 3.84 (td, *J* = 9.2, 6.4 Hz, 1H), 3.69 – 3.58 (m, 2H), 3.11 – 3.03 (m, 0H), 2.89 – 2.82 (m, 1H), 2.69 – 2.54 (m, 1H), 2.49 – 2.41 (m, 1H), 2.24 – 2.13 (m, 2H), 2.08 (dt, *J* = 14.4, 6.8 Hz, 1H), 1.75 – 1.67 (m, 3H), 1.54 – 1.51 (m, 1H), 1.36 – 1.22 (m, 2H), 1.20 – 1.11 (m, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.7 (d, *J* = 11.4 Hz), 162.0 (d, *J* = 11.3 Hz), 148.8 , 141.3 (t, *J* = 8.0 Hz), 129.4 , 115.1 , 111.9 (dd, *J* = 21.7, 6.5 Hz), 110.9 , 109.4 (t, *J* = 24.9 Hz), 58.6 , 54.7 , 43.0 , 36.2 , 32.2 , 29.6 , 26.0 , 25.7 , 25.7 , 24.7 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.01 – -105.04 (m)



2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazepane, 7_{cis}: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116.6 mg, 0.5 mmol, 1 equiv), 1-phenyl piperidine (450 µl, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (6.4 mg, 0.005 mmol, 0.01 equiv) provided the product (128.8 mg, 64% yield) as a clear oil after purification by flash column chromatography (0% ethyl acetate:hexanes to 20% ethyl acetate:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 – 7.32 (m, 2H), 7.19 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.07 – 6.97 (m, 1H), 6.72 (d, *J* = 8.3 Hz, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 3.86 (dt, *J* = 10.4, 6.9 Hz, 1H), 3.63 – 3.52 (m, 2H), 3.06 (dd, *J* = 15.6, 11.4 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.41 – 2.30 (m, 2H), 2.23 (dp, *J* = 11.9, 4.1 Hz, 1H), 2.15 (dtd, *J* = 12.0, 7.9, 4.1 Hz, 1H), 2.08 (dt, *J* = 14.4, 7.2 Hz, 1H), 1.77 – 1.66 (m, 3H), 1.60 – 1.52 (m, 1H), 1.37 – 1.22 (m, 2H), 1.22 – 1.13 (m, 1H).

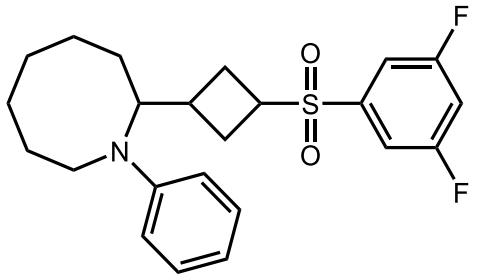
^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.7 , 163.6 , 162.0 , 148.5 , 141.4 , 141.3 , 141.3 , 129.4 , 115.1 , 112.0 , 111.9 , 111.8 , 111.8 , 110.8 , 109.5 , 109.4 , 109.2 , 58.6 , 53.2 , 43.2 , 34.3 , 31.9 , 29.8 , 26.9 , 26.3 , 25.9 , 24.8 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.95 – -104.96 (m).

Crystal Experimental. Single colorless prism-shaped crystals of **7_{cis}** were recrystallised from diethyl ether and hexane by vapor diffusion. A suitable crystal 0.55×0.32×0.23 mm^3 was selected and mounted on a loop with paratone oil on an XtaLAB Synergy-S diffractometer. The crystal was kept at a steady *T* = 102(4) K during data collection. The structure was solved with the **ShelXT** (Sheldrick,

2015) structure solution program using the Intrinsic Phasing solution method and by using **Olex2** (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2018/3 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{22}H_{25}F_2NO_2S$, M_r = 405.49, monoclinic, $P2_1/n$ (No. 14), a = 9.56610(10) Å, b = 21.4256(3) Å, c = 19.3969(2) Å, β = 96.1240(10)°, $\alpha = \gamma = 90°$, V = 3952.89(8) Å^3, T = 102(4) K, Z = 8, Z' = 2, μ(MoK$_\alpha$) = 0.200, 135731 reflections measured, 20640 unique (R_{int} = 0.0684) which were used in all calculations. The final wR_2 was 0.1495 (all data) and R_1 was 0.0566 (I > 2σ(I)).



2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazocane, 8: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116 mg, 0.5 mmol, 1 equiv), 1-phenylpyrrolidine (472 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF$_6$ (6.2 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (202 mg, 96% yield, 3:7 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (15% ethyl acetate:hexanes).

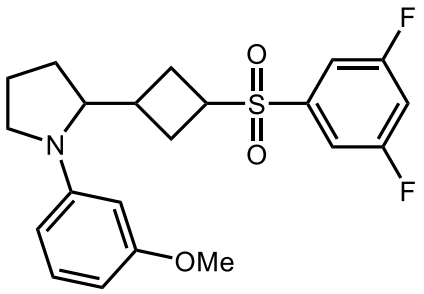
For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.42 – 7.38 (m, 2H$_a$), 7.37 – 7.34 (m, 2H$_b$), 7.25 – 7.21 (m, 2H$_b$), 7.21 – 7.16 (m, 2H$_a$), 7.08 (tt, J = 8.3, 2.4 Hz, 1H$_a$ + 1H$_b$), 6.82 (d, J = 8.4 Hz, 2 H$_b$), 6.78 (d, J = 8.4 Hz, 2 H$_a$), 6.65 (t, J = 7.2 Hz, 1H H$_b$), 6.61 (t, J = 7.2 Hz, 1H H$_a$), **3.93 (ddd, J = 11.8, 8.5, 3.8 Hz, 1H$_b$), 3.86 (td, J = 10.3, 3.9 Hz, 1H$_a$)**, 3.66 (tt, J = 9.6, 5.1 Hz, 1 H$_a$), 3.59 (p, J = 8.6 Hz, 1

H_b), 3.52 (ddd, *J* = 15.5, 4.7, 2.7 Hz, 1 H_a), 3.49 – 3.44 (m, 1 H_b), 3.26 – 3.12 (m, 1H_a + 1H_b), 2.77 (dtd, *J* = 16.4, 9.3, 6.9 Hz, 1 H_a), 2.69 (dtd, *J* = 13.0, 6.1, 2.8 Hz, 1 H_a), 2.44 (h, *J* = 8.5 Hz, 1 H_b), 2.40 – 2.30 (m, 1H_a + 1H_b), 2.29 – 2.22 (m, 2H_b), 2.13 (ddd, *J* = 13.0, 8.6, 6.8 Hz, 1Ha), 2.09 – 2.02 (m, 1H_a + 1H_b), 1.96 (ttd, *J* = 18.2, 10.2, 9.3, 5.4 Hz, 1H_a +1H_b), 1.77 – 1.36 (m, 9H_a + 9H_b).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.7 (dd, *J* = 11.5, 6.0 Hz), 162.0 (dd, *J* = 11.3, 5.9 Hz), 148.8 , 148.4 , 142.3 – 141.0 (m), 129.4 , 129.3 , 115.4 , 115.3 , 112.0 – 111.6 (m), 109.3 (td, *J* = 24.9, 7.7 Hz), 60.6 , 60.0 , 54.3 , 53.0 , 42.2 , 41.6 , 35.3 , 33.6 , 27.3 , 27.0 (d, *J* = 2.2 Hz), 26.8 , 26.5 , 26.5 , 26.4 , 26.2 , 26.2 , 25.8 , 25.8 , 25.4 , 24.9 , 24.6 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.98 (dd, *J* = 8.5, 5.2 Hz), -105.03 (dd, *J* = 8.3, 5.3 Hz).



2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-(3-methoxyphenyl)pyrrolidine, 9:

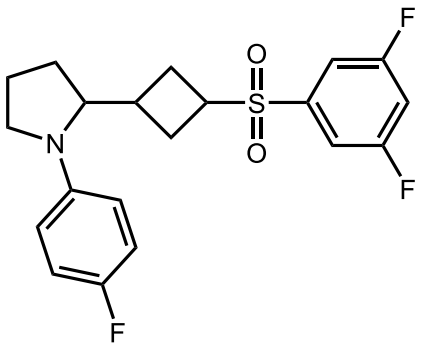
Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115 mg, 0.5 mmol, 1 equiv), 1-(3-methoxyphenyl)pyrrolidine (443 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (124 mg, 61% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (0% ethyl acetate:hexanes to 50% ethyl acetate:hexanes).

For the mixture of isomers:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.40 (tp, *J* = 9.3, 7.7, 2.2 Hz, $2H_{a+}$ $2H_b$), 7.15 – 7.04 (m, $2H_{a+}$ $2H_b$), 6.29 – 6.13 (m, $3H_{a+}$ $3H_b$), **3.90 – 3.83 (m, $1H_{a+}$ $1H_b$)**, 3.79 (d, *J* = 12.0 Hz, $3H_{a+}$ $3H_b$), 3.70 – 3.40 (m, $2H_{a+}$ $2H_b$), 3.20 – 3.09 (m, $1H_{a+}$ $1H_b$), 2.96 (h, *J* = 8.3 Hz, $1H_a$), 2.61 – 2.09 (m, $4H_{a+}$ $5H_b$), 1.95 (dddd, *J* = 22.9, 10.5, 7.8, 4.8 Hz, $3H_{a+}$ $4H_b$), 1.73 (dt, *J* = 11.4, 4.2 Hz, $1H_a$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.9 , 161.9 , 160.7 , 150.1 , 149.3 , 141.3 , 129.8 , 112.3 – 111.3 (m), 109.4 (t, *J* = 24.8 Hz), 105.8 , 105.6 , 100.9 , 99.2 , 99.0 , 60.2 , 60.0 , 55.1 , 54.9 , 53.2 , 50.1 , 49.3 , 36.5 , 33.7 , 28.6 , 27.8 , 27.0 , 25.8 , 25.7 , 23.8 , 23.8 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.95 (dd, *J* = 8.7, 5.1 Hz), -104.99 (dd, *J* = 8.5, 5.4 Hz).



2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-(4-fluorophenyl)pyrrolidine, 10:

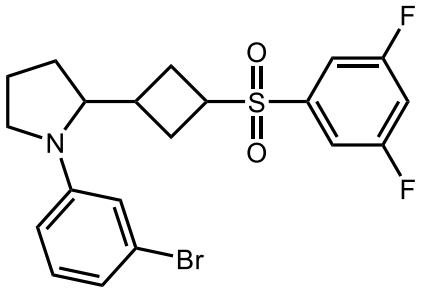
Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115 mg, 0.5 mmol, 1 equiv), 1-(4-fluorophenyl)pyrrolidine (413 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (168 mg, 79% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (0% ethyl acetate:hexanes to 50% ethyl acetate:hexanes).

For the mixture of isomers:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 (ddd, *J* = 18.9, 4.9, 2.5 Hz, $2H_{a+}$ $2H_b$), 7.08 (tdd, *J* = 8.4, 5.0, 1.9 Hz, $1H_{a+}$ $1H_b$), 6.91 (q, *J* = 8.6 Hz, $2H_{a+}$ $2H_b$), 6.53 (td, *J* = 9.2, 4.3 Hz, $2H_{a+}$ $2H_b$), **3.85 – 3.75 (m, $1H_{a+}$ $1H_b$)**, 3.70 – 3.41 (m, $2H_{a+}$ $2H_b$), 3.08 (p, *J* = 8.8 Hz, $1H_{a+}$ $1H_b$), 2.97 (q, *J* = 8.1 Hz, $1H_a$), 2.62 – 2.04 (m, $4H_{a+}$ $5H_b$), 1.95 (dp, *J* = 20.8, 6.8, 6.1 Hz, $3H_{a+}$ $4H_b$), 1.80 – 1.70 (m, $1H_a$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.9 (d, *J* = 11.5 Hz), 161.8 (d, *J* = 11.3 Hz), 156.0 , 154.1 , 145.4 , 144.7 , 141.4 , 115.5 (d, *J* = 4.4 Hz), 115.4 (d, *J* = 4.4 Hz), 113.2 (d, *J* = 7.2 Hz), 112.9 (d, *J* = 7.2 Hz), 112.4 – 111.6 (m), 109.4 (t, *J* = 25.0 Hz), 60.5 , 60.4 , 54.9 , 53.2 , 50.7 , 50.0 , 36.2 , 33.7 , 28.5 , 28.0 , 26.9 , 25.7 , 25.6 , 25.5 , 24.0 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.90 (dd, *J* = 8.6, 5.3 Hz), -104.96 (dd, *J* = 8.4, 5.1 Hz), -129.62 (tt, *J* = 8.5, 4.3 Hz), -129.82 (tt, *J* = 8.4, 4.3 Hz).



1-(3-bromophenyl)-2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pyrrolidine, 11:

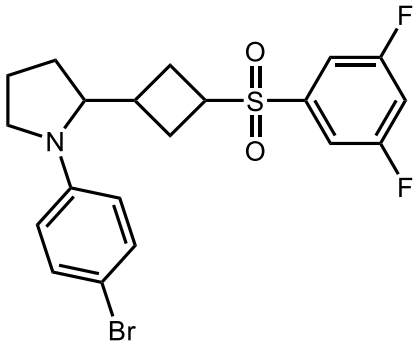
Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (114.8 mg, 0.5 mmol, 1 equiv), 1-(3-bromophenyl)pyrrolidine (565 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5.8 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (130 mg, 57% yield, 7:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (10% ethyl acetate:hexanes).

For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-d) δ 7.27 (ddd, J = 20.9, 4.4, 2.0 Hz, $2H_{a+}$ $2H_{b}$), 7.17 – 7.10 (m, $2H_{a+}$ $2H_{b}$), 6.95 (tdq, J = 8.3, 4.0, 2.0 Hz, $1H_{a+}$ $1H_{b}$), 6.35 (t, J = 8.9 Hz, $2H_{a+}$ $2H_{b}$), **3.75 – 3.64 (m, $1H_{a+}$ $1H_{b}$)**, 3.64 – 3.28 (m, $2H_{a+}$ $2H_{b}$), 2.90 (dq, J = 69.5, 9.0, 8.3 Hz, $1H_{a}$), 2.46 – 1.96 (m, $4H_{a+}$ $5H_{b}$), 1.92 – 1.71 (m, $3H_{a+}$ $4H_{b}$), 1.65 – 1.61 (m, $1H_{a}$).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.8 , 163.7 , 162.1 , 162.0 , 147.6 , 146.9 , 141.4 , 141.3 , 131.8 , 131.7 , 114.1 , 113.9 , 112.0 , 111.9 , 111.7 , 109.6 , 109.4 , 109.2 , 108.0 , 108.0 , 60.2 , 60.1 , 54.9 , 53.2 , 50.1 , 49.4 , 36.3 , 33.6 , 28.5 , 27.9 , 27.0 , 25.8 , 25.7 , 25.6 , 23.9 , 23.8 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.78 – -104.84 (m), -104.88 – -104.95 (m).



1-(4-bromophenyl)-2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pyrrolidine, 12:

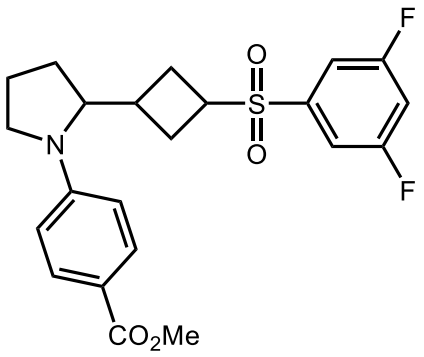
Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (69.0 mg, 0.3 mmol, 1 equiv), 1-(4-bromophenyl)pyrrolidine (334 mg, 1.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (3.3 mg, 0.003 mmol, 0.01 equiv) provided the product as a mix of diastereomers (75 mg, 71% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear brown oil after purification by flash column chromatography (10% ethyl acetate:hexanes).

For the mixture of isomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, $2H_{a+}$ $2H_b$), 7.30 – 7.22 (m, $2H_{a+}$ $2H_b$), 7.16 – 7.04 (m, $1H_{a+}$ $1H_b$), 6.48 (t, *J* = 9.6 Hz, $2H_{a+}$ $2H_b$), **3.87 – 3.79** (m, **$1H_{a+}$ $1H_b$**), 3.64 (tt, *J* = 9.2, 4.5 Hz, $1H_a$), 3.58 (ddd, *J* = 17.1, 9.4, 7.8 Hz, $1H_b$), 3.50 (dt, *J* = 10.0, 5.0 Hz, $1H_a$), 3.46 – 3.42 (m, $1H_b$), 3.14 – 3.05 (m, $1H_{a+}$ $1H_b$), 3.02 – 2.93 (m, $1H_a$), 2.58 – 2.44 (m, $1H_{a+}$ $1H_b$), 2.43 – 2.09 (m, $3H_{a+}$ $4H_b$), 2.06 – 1.89 (m, $3H_{a+}$ $4H_b$), 1.79 – 1.72 (m, $1H_a$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 163.9 (d, *J* = 11.5 Hz), 161.9 (d, *J* = 11.3 Hz), 147.5 , 146.9 , 141.4 , 131.7 , 131.7 , 114.1 , 114.0 , 112.3 – 111.5 (m), 109.4 (t, *J* = 24.9 Hz), 60.2 , 60.1 , 54.8 , 53.2 , 50.1 , 49.4 , 36.2 , 33.6 , 28.5 , 27.9 , 27.0 , 25.8 , 25.7 , 25.6 , 23.8 , 23.8 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.80 (dd, *J* = 8.3, 5.6 Hz), -104.91 (dd, *J* = 8.3, 5.5 Hz).



methyl 4-(2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pyrrolidin-1-yl)benzoate, 13:

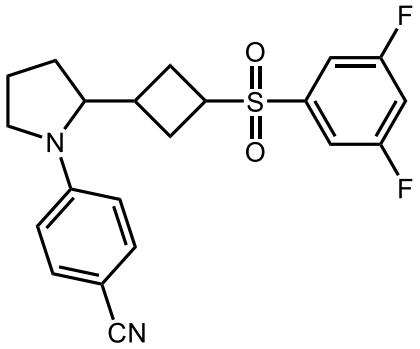
Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115 mg, 0.5 mmol, 1 equiv), methyl 4-(pyrrolidin-1-yl)benzoate (513 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (168 mg, 77% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (0% ethyl acetate:hexanes to 50% ethyl acetate:hexanes).

For the mixture of isomers:

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 11.9, 8.4 Hz, $2H_{a+}$ $2H_b$), 7.50 – 7.33 (m, $2H_{a+}$ $2H_b$), 7.07 (tq, *J* = 8.5, 2.7 Hz, $1H_{a+}$ $1H_b$), 6.56 (t, *J* = 8.8 Hz, $2H_{a+}$ $2H_b$), **4.02 – 3.92 (m, $1H_{a+}$ $1H_b$)**, 3.88 – 3.80 (m, $3H_{a+}$ $3H_b$), 3.70 – 3.45 (m, $1H_{a+}$ $2H_b$), 3.20 (q, *J* = 8.6 Hz, $1H_{a+}$ $1H_b$), 2.98 (p, *J* = 8.5 Hz, $1H_a$), 2.60 – 2.09 (m, $5H_{a+}$ $5H_b$), 2.07 – 1.90 (m, $4H_{a+}$ $4H_b$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.3 , 167.3 , 163.8 , 161.8 (d, *J* = 11.6 Hz), 151.5 , 150.9 , 141.3 , 131.3 , 131.3 , 117.2 , 112.3 – 111.6 (m), 111.5 , 111.4 , 109.4 (t, *J* = 24.9 Hz), 60.2 , 60.0 , 54.7 , 53.0 , 51.5 , 49.3 , 48.8 , 36.2 , 33.4 , 28.4 , 27.8 , 27.1 , 26.1 , 25.7 , 23.6 , 23.4.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.75 (dd, *J* = 8.2, 5.4 Hz), -104.85 (dd, *J* = 8.2, 5.3 Hz).



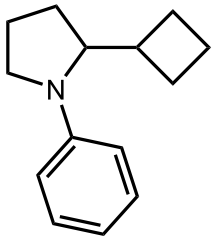
4-(2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)pyrrolidin-1-yl)benzonitrile, 14: Following the general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (114.6 mg, 0.5 mmol, 1 equiv), 4-(Pyrrolidin-1-yl)benzonitrile (432 mg, 2.5 mmol, 5 equiv), and Ir[dF(CF3)ppy]2(dtbbpy)PF6PF_6 (5.7 mg, 0.005 mmol, 0.01 equiv) provided the product as a mix of diastereomers (180 mg, 90% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow foam after purification by flash column chromatography (35% ethyl acetate:hexanes).

For the mixture of isomers:

1H NMR (600 MHz, Chloroform-d) δ 7.43 – 7.33 (m, $4H_a$ + $4H_b$), 7.06 (tq, J = 8.3, 2.3 Hz, $1H_a$ + $1H_b$), 6.55 (dd, J = 9.1, 2.3 Hz, $2Ha$ + $2H_b$), 3.93 (tdd, J = 9.5, 6.3, 2.3 Hz, $1H_a$ + $1H_b$), **3.63 (ttd, J = 9.5, 4.2, 1.1 Hz, $1H_a$), 3.56 (tt, J = 9.3, 7.8 Hz, $1H_b$)**, 3.52 – 3.44 (m, $1H_a$ + $1H_b$), 3.18 (p, J = 8.7 Hz, $1H_a$ + $1H_b$), 2.98 (dq, J = 16.4, 8.7 Hz, $1H_a$), 2.57 – 2.45 (m, $1H_a$ + $1H_b$), 2.42 – 2.08 (m, $4H_a$ + $4H_b$), 2.06 – 1.92 (m, $2H_a$ + $4H_b$), 1.82 – 1.76 (m, $1H_a$).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.7 , 162.0 , 150.7 , 150.3 , 141.3 , 133.4 (d, *J* = 3.9 Hz), 120.5 , 112.2 , 112.2 , 111.7 (td, *J* = 22.6, 6.6 Hz), 109.4 (t, *J* = 24.9 Hz), 97.5 , 60.2 , 60.1 , 54.6 , 52.9 , 49.1 , 48.7 , 35.8 , 33.2 , 28.2 , 27.8 , 27.0 , 26.1 , 25.7 , 25.5 , 23.4 , 23.3 .

^{19}F NMR (376 MHz, Chloroform-*d*) δ -113.87 (t, *J* = 7.0 Hz), -114.17 (t, *J* = 7.0 Hz).



2-cyclobutyl-1-phenylpyrrolidine, 15: Following the general procedure B, the reaction of 2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpyrrolidine (140 mg, 0.38 mmol, 1 equiv) and magnesium turnings (380 mg, 15 mmol, 40 equiv) provided the product (54 mg, 71% yield) as a clear oil after purification by flash column chromatography (5% ethyl acetate:hexanes).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.23 – 7.16 (m, 2H), 6.62 (d, *J* = 9.1 Hz, 3H), 3.80 – 3.69 (m, 1H), 3.49 – 3.42 (m, 1H), 3.10 (q, *J* = 9.3 Hz, 1H), 2.57 (dq, *J* = 15.0, 7.4 Hz, 1H), 2.03 – 1.63 (m, 10H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 148.6, 128.9, 115.3, 112.2, 61.0, 49.3, 40.8, 28.3, 26.5, 25.4, 23.9, 18.6.

3.5 Chapter Three References

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Chapter 4:

Synthesis of Spirocyclic Piperidines by Radical Hydroarylation

Figure 4.1 Final Jui group picture taken.

Reprinted with permission from (R. M. Spurlin, A. L. Harris, **C. J. Pratt**, and N. T. Jui Synthesis of Spirocyclic Piperidines by Radical Hydroarylation. Synlett. 2020, 32, 211–214.)

4.1 Introduction

In previous chapters we have clearly outlined the power of the alpha amino radical as a coupling partner for various new partners. In this chapter we assign the amine a new and equally important role as shown in Figure 4.2. In this chapter, the amine will not be a substrate but will instead act as a source of electrons to achieve more difficult reductions. As proposed in previous mechanisms, the amine can donate an electron (pink) to the catalyst. This form of the catalyst is a radical anion and the electron (green) present in the high energy single occupied molecular orbital can become a potent reductant. In particular, the reduction of aryl iodides will be shown to access an array of high-value (hetero)aryl spiropiperidine compounds.

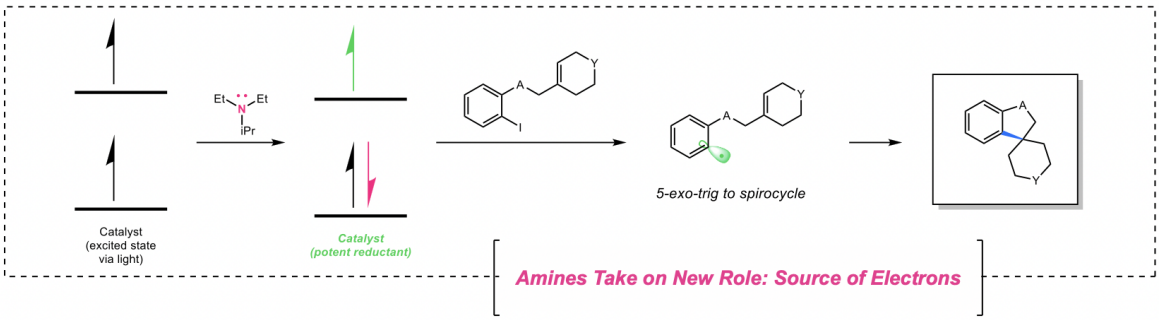


Figure 4.2 Amines take on a new role in this chapter.

Piperidine itself holds a privileged position in the pharmaceutical landscape. In fact, it is the most common structural component found across all U.S. FDA approved drugs.[41,99] The aforementioned (hetero)aryl spiropiperidine scaffold is of particular interest to us because it is considered a privileged structure and has found utility as pharmacophore templates across a range of different biological targets. This is due largely to the structural rigidity provided by the fused rings that in turn enables the projection of functional groups in a well-defined manner. As a result, the spiropiperidine is gaining prevalence as a template in drug discovery.

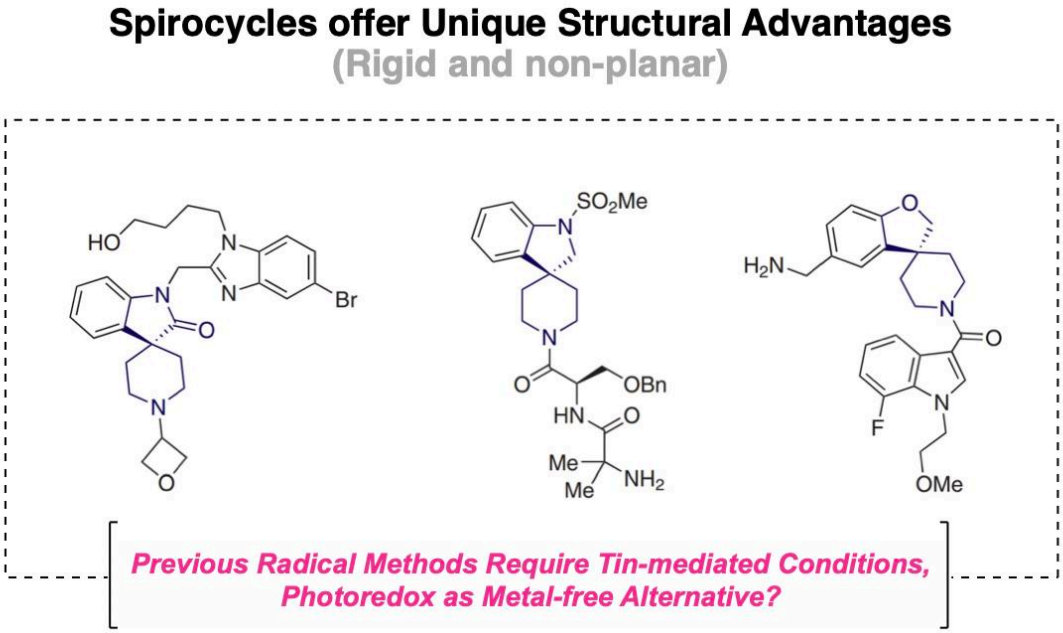


Figure 4.3 A collection of spirocyclic piperidine containing drugs.

Figure 4.3 shows a select collection of bioactive spiropiperidines in which the piperidine units are bound to various saturated heterocycles.[100-102] Considerable success has been achieved in the synthesis of spiropiperidine derivatives including using dehydration, nucleophilic aromatic substitution, Friedel-Crafts, dialkylation reactions, a Fischer-indoline type synthesis, and palladium α-arylation. Specifically for the molecules shown above, the left most molecule is a RSV fusion inhibitor and was prepared by using enolate arylation.[100] The middle compound is a spiroindoline growth hormone secretagogue and was obtained by means of a Fisher-type condensation/rearrangement sequence of a hydrazine building block.[101] Finally, assembly of a similar spirocyclic framework in a β-tryptase inhibitor was performed by using a tin-mediated radical-chain mechanism.[102,103] This last method caught our attention. We questioned if photoredox catalysis powered by an organic catalyst could serve as an alternative radical centered route that would utilize modular starting materials and enable the formation of the challenging all carbon quaternary center under mild and metal-free conditions.[35]

We felt particularly situated to achieve this goal because our laboratory had previously developed a series of olefin hydroarylation methods that utilized the highly reactive nature of aryl radicals.[65,104,105] In particular, the work from Autumn Flynn and Kelly McDaniel had been used to access similar looking structures. However, access to the spiropiperidine would need to come from a pyridine containing substrate and, in these cases, spirocyclization was not observed. To overcome this limitation, we used linear precursors like those found in the tin-based radical methods (easily accessible through heteroatom alkylation). These we suspected would undergo radical formation through catalytic single-electron transfer (SET) and then regioselective cyclization and radical termination through hydrogen-atom transfer (HAT) would then provide the desired spiropiperidine. This net reductive machinery is appealing, in comparison with the previously outlined tin-method, because it is driven by visible light and a commercial nontoxic amine (it should also be noted that the only byproducts of the mechanism are ammonium iodide).

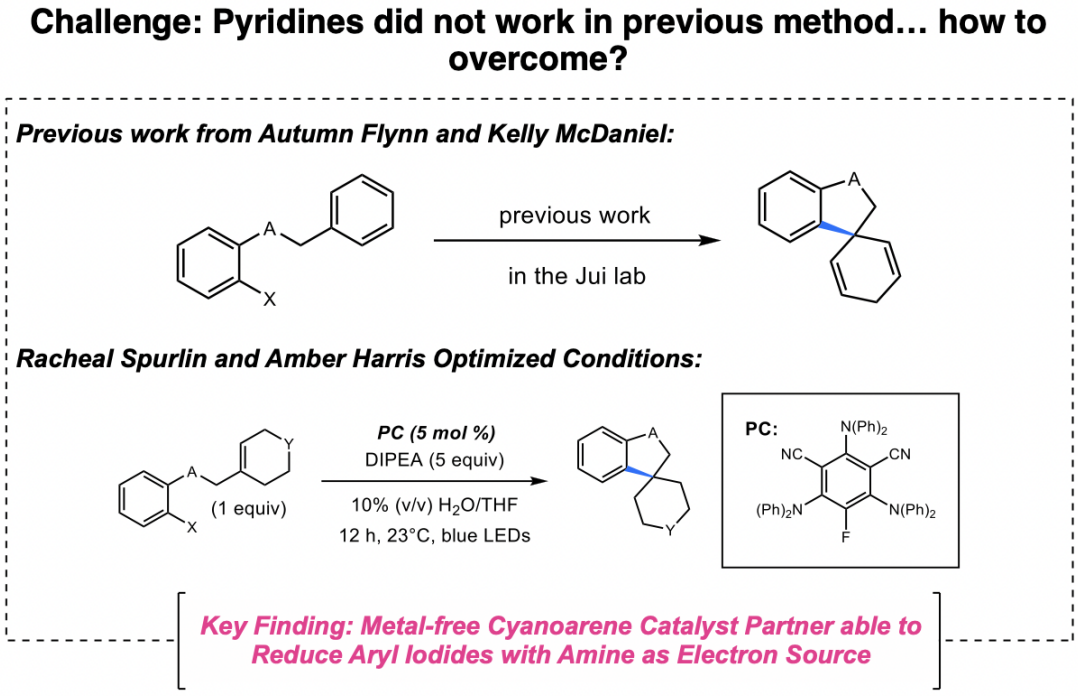
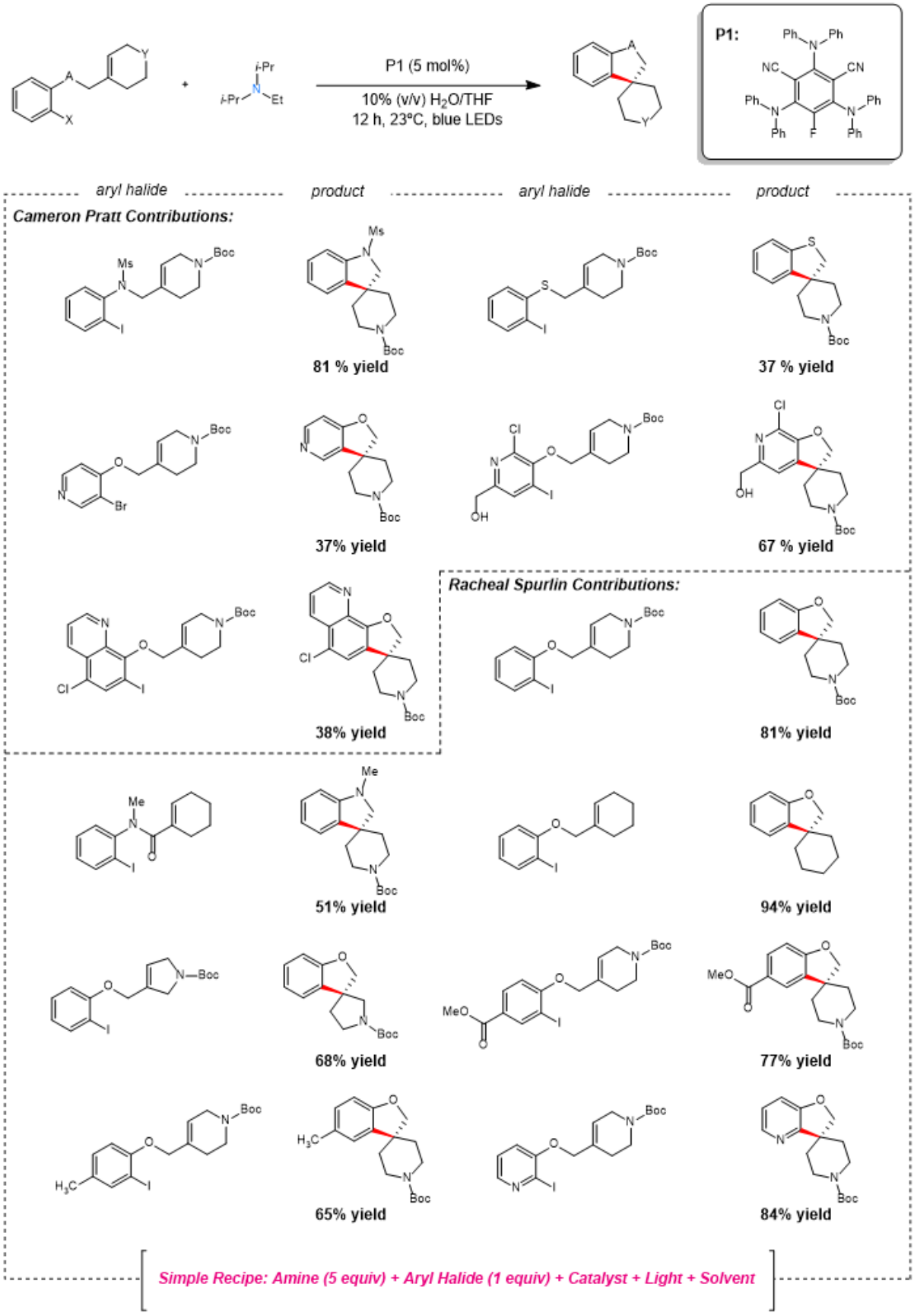


Figure 4.4 Overcoming previous method's limitations.

4.2 Results and Discussion

After a brief optimization from our previous spiro-dearomatization conditions (completed by Amber Harris and Racheal Spurlin), we were pleased to find the desired spirocyclic product was formed when using 3DPAFIPN, Hüing's base, and a 10% H_2O/THF solvent system. To probe the generality of this system, we tested alterations of the linker heteroatom, the tethered radical precursor, and the radical acceptor as shown in Table 4.1. The author showcased first how a mesyl-protected and sulfur linker could undergo cyclization in an 81% and 37% yield, respectively. Pyridyl substrates with halogenation at the 3-position triggered reductive cyclization to afford the complex triheterocyclic systems in a modest yield of 37%. Of particular note was the ability of the highly functionalized pyridine in this system to undergo selective activation of the Ar-I bond in the presence of the Ar-Cl (due do C–X bond strength)[106]. It also showcased the inherent ability of the key radical intermediate to couple with olefins in the presence of acidic and polar functional groups such as alcohols at an impressive 67% yield. Finally, the author underlined the former point by the reductive cyclization of 7-iodo-5-chloroquinoline to give 12 in a 38% yield. Racheal Spurlin also contributed to showing various linker atoms that could be tolerated. Under this system, ether-linked substrates were transformed into the corresponding dihydrofuran-fused piperidine structures in an impressive 81% yield. This scaffold is of particular note because it has been evaluated extensively for its ability to modulate opioid receptors.[107,108] In addition, the methylated nitrogen linker smoothly cyclized to afford the spiro indoline in a 51% yield. As expected, other cyclic olefins reacted similarly, with exoselective hydroarylation of cyclohexene and dihydropyrrole substrates giving rise to the desired products in 94% and 68% yield respectively. Iodophenol derivatives containing substituents at the 4-position were good substrates under the standard conditions, and products with an ester and methyl group were obtained in yields of 77 and 65%, respectively. Finally, the tin-free reduction of a pyridyl substrate with iodination at the 2-position was also be achieved with an 84% yield.

Table 4.1 Organic photoredox spirocyclization: substrate scope



We envision the cyclization of this system to go through a radical hydroarylation process, as seen in Figure 4.4. Photoexcitation of the donor–acceptor cyanoarene catalyst P1 (3DPAFIPN) is followed by reductive quenching with Hünig's base [$E_{1/2^{red}}$ = 0.84 V vs. SCE ($P1^*$: $E_{1/2^{red}}$ = +1.09 V vs. SCE)].[12,109] Single electron transfer from the resulting-ground state reductant ($P1^{\bullet-}$: $E_{1/2^{red}}$ = –1.59 V vs. SCE)[12] to the aryl halide 1, followed by rapid halide expulsion from the aryl radical anion, gives rise to radical species 2. This species can undergo 5-*exo-trig* cyclization to form 3. The alkyl radical is terminated with a hydrogen atom transfer (HAT) from the radical amine, to give the hydroarylation product 4. Evidence supporting this proposal includes a high observed rate of excited photocatalyst luminescence quenching by the amine base (KSV ≈1700),[110] indicating that radical formation probably occurs through a reductive quenching pathway.[110] To probe the nature of radical termination in this

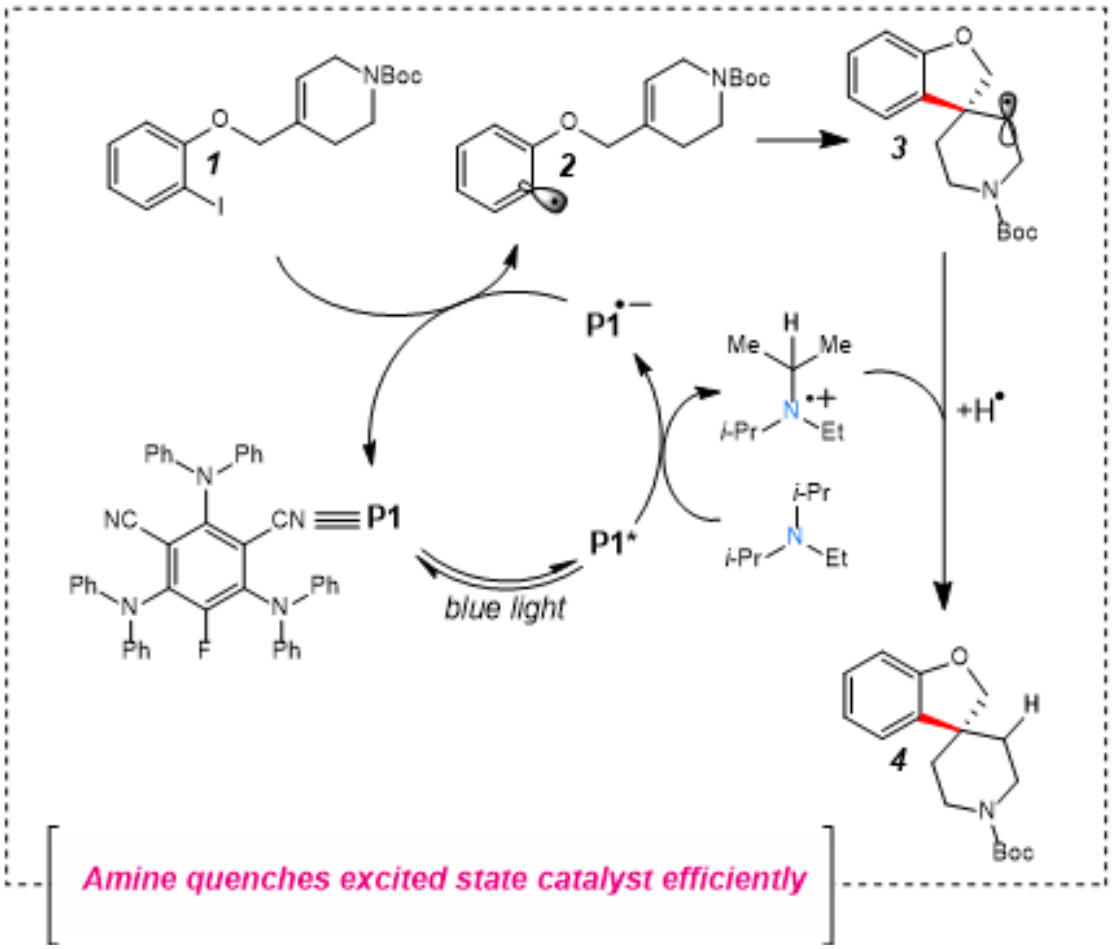


Figure 4.4 Proposed mechanism of the metal-free hydroarylation

process, the author and Racheal conducted a series of isotopic labeling studies. It was found that when the amine reductant was replaced with triethylamine-d_{15}, deuterium transfer occurred from this amine to product 4, albeit with moderate fidelity (~1:1 D/H). Some proton incorporation presumably occurs through HAT from the THF solvent. As shown in previous chapters, the radical termination could, in principle, occur through one electron reduction and protonation of the resulting anion. But in this case, deuterium incorporation was not observed when the reaction was conducted in the presence of D_2O.

4.3 Conclusion

In summary, we have designed a simple photocatalytic system that enables a generalized scaffold of intermediates to undergo radical spirocyclization furnishing spiropiperidines. This process is a mild, metal-free reaction, requiring only blue light and an amine as stoichiometric inputs. Regioselective cyclization and radical termination through HAT affords the desired scaffolds, and substitution of the aryl radical precursor, linking alkyl unit, and cyclic olefin are all shown to be well tolerated, affording a wide range of complex spiro-fused heterocycles.

4.4 Supporting Information

4.4.1 General Information

Solvents used in anhydrous reactions were purified by passing over activated alumina and storing under argon. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Combi-Blocks, Oakwood Chemicals, TCI America, and Cambridge Isotopes and used as received, unless stated otherwise. Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on 230–400 mesh silica gel. Thin-layer chromatography (TLC) was performed on 250 μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed

by fluorescence quenching or staining using a KMnO4 stain. Solvent was degassed by sonication under mild vacuum for 15 minutes. Photoredox catalysts 3DPAFIPN was prepared according to the literature procedure.[12]

All yields refer to chromatographically and spectroscopically (1H NMR) homogenous materials. New compounds were characterized by NMR and LCMS. 1H and 13C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), or VNMR 400 (400 MHz), and are internally referenced to residual protio solvent signals. Data for 1H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, b= broad), coupling constant (Hz), and integration, when applicable. Data for decoupled 13C NMR are reported in terms of chemical shift and multiplicity when applicable. Liquid Chromatography Mass Spectrometry (LC-MS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet.

4.4.2 General Procedures

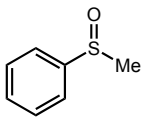
General Coupling Procedure A: A round bottom flask was charged with aryl halide (1.1 equiv) and K2CO3 (2.0 equiv). The round bottom was equipped with a stir bar and was sealed with a red septum stopper. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DMF (0.1 M) was added via syringe followed by tert-butyl 4- (chloromethyl-3,6- dihydropyridine- 1(2H)-carboxylate (1.0 equiv). The resulting mixture was stirred at 70 °C for 12 h before being cooled to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water (1x 100 mL) and brine (3x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary

evaporation. The residue was purified on silica using the indicated solvent mixture as eluent to afford the product.

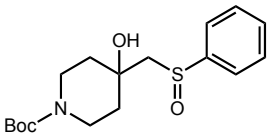
General Coupling Procedure B: A round bottom flask was charged with aryl halide (1.1 equiv) and K2CO3 (2.0 equiv). The round bottom was equipped with a stir bar and was sealed with a red septum stopper. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, DMF (0.1 M) was added via syringe followed by tert-butyl 4- (chloromethyl-3,6- dihydropyridine- 1(2H)-carboxylate (1.0 equiv). The resulting mixture was stirred at 70 °C for 12 h before being cooled to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water (1x 100 mL), 1M NaOH (2x 100mL), and brine (3x 100mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation to give the title compound with no further purification required.

General Photoredox Procedure: A 16 mL screw-top test tube was charged with substrate (0.3 mmol, 1.0 equiv) and photocatalyst (0.015 mmol, 5 mol%). The tube was equipped with a stir bar and was sealed with a PTFE/silicon septum. The atmosphere was exchanged by applying vacuum and backfilling with nitrogen (this process was conducted a total of three times). Under nitrogen atmosphere, separated degassed solvent was added via syringe (5.4 mL of THF and 0.6 mL of DI H2O to give a 0.05 M solution), followed by diisopropylethylamine (1.5 mmol, 5.0 equiv). The resulting mixture was stirred at 800 RPM for 16 h under the irradiation by blue LEDs. The reaction mixture was then diluted with water and extracted with ethyl acetate (3x 20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated via rotary evaporation. The residue was purified on silica using the indicated solvent mixture as eluent to afford the product.

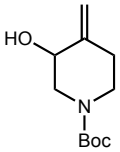
4.4.3 Preparation of Starting Materials



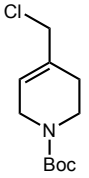
(methylsulfinyl)benzene (S1): The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[111]



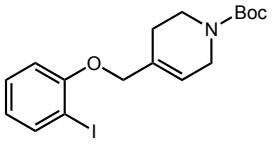
***tert*-butyl 4-hydroxy-4-((phenylsulfinyl)methyl)piperidine-1-carboxylate (S2):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported. [112]



***tert*-butyl 3-hydroxy-4-methylenepiperidine-1-carboxylate (S3):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported. [112]



***tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S4):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[112]

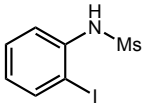


***tert*-butyl 4-((2-iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S5):** Following general procedure A, the reaction of 2-iodophenol (209 mg, 0.95 mmol, 1.1 equiv), K_2CO_3 (357 mg, 2.6 mmol, 2.0 equiv), *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (200.1 mg, 0.86 mmol, 1.0 equiv), and DMF (8.6 mL) provided the title compound (270 mg, 76% yield) as a white solid after purification by flash column chromatography (10-20% EtOAc/Hex eluent).

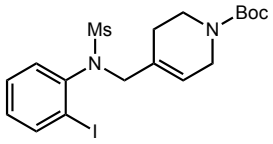
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 8.7, 7.5 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.71 (td, *J* = 7.6, 2.3 Hz, 1H), 5.85 (s, 1H), 4.47 (s, 2H), 3.95 (s, 2H), 3.56 (s, 2H), 2.25 (s, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.06, 154.91, 139.51, 132.09, 129.42, 122.76, 112.41, 86.66, 79.67, 72.04, 43.35, 39.87 28.49, 25.83.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{23}INO_3$: 416.1, found 316.1 (**S5**-Boc)



***N*-(2-iodophenyl)methanesulfonamide (S6):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[113]

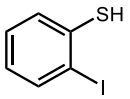


***tert*-butyl 4-((*N*-(2-iodophenyl)methylsulfonamido)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S7):** Following general procedure A, the reaction of *N*-(2-iodophenyl) methanesulfonamide (328 mg, 1.1 mmol, 1.1 equiv), K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv), *tert*-butyl 4- (chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (231.7 mg, 1.0 mmol, 1.0 equiv), and DMF (10 mL) provided the title compound (318 mg, 65% yield) as a yellow oil after purification by flash column chromatography (20-50% EtOAc/Hex eluent).

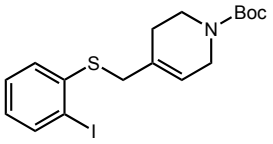
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (t, *J* = 6.8 Hz, 1H), 7.35 (m, 2H), 7.06 (d, *J* = 7.1 Hz, 1H), 5.37 (s, 1H), 4.30 (d, *J* = 14.7 Hz, 1H), 4.13 (d, *J* = 14.0 Hz, 1H), 3.75 (t, *J* = 18.0 Hz, 2H), 3.50 (d, *J* = 12.6 Hz, 1H), 3.42 (s, 1H), 3.08 (s, 3H), 2.27(s, 2H), 1.44 (s, 9H)

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.97, 140.75, 132.78, 130.32, 129.32, 100.52, 79.80, 60.53, 56.64, 41.28, 31.73, 29.71, 28.59, 27.06, 22.79, 14.26.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{18}H_{26}IN_2O_4S$: 493.1, found 393.0 (**S7**-Boc)



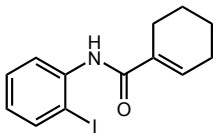
2-iodobenzenethiol (S8): The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[114]



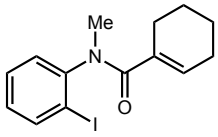
***tert*-butyl 4-(((2-iodophenyl)thio)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S9):** Following general procedure A, the reaction of 2-iodobenzenethiol (924 mg, 3.9 mmol, 1.3 equiv), K_2CO_3 (801 mg, 5.8 mmol, 2.0 equiv), *tert*-butyl 4- (chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (671.9 mg, 2.9 mmol, 1.0 equiv), and DMF (29 mL) provided the title compound (964 mg, 77% yield) as a clear oil after purification by flash column chromatography (10-20% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.37 – 7.26 (m, 2H), 6.88 (td, *J* = 7.3, 1.8 Hz, 1H), 5.52 (s, 1H), 3.82 (s, 2H), 3.53 (s, 2H), 3.49 (s, 2H), 2.25 (s, 2H), 1.46 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 154.66, 140.83, 139.43, 131.11, 129.33, 128.42, 127.32, 123.49, 122.31, 101.31, 79.46, 41.24, 40.89, 28.33, 27.37.

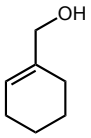
LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{23}INO_2S$: 432.0, found 376.1 (**S9**-*t*Bu)



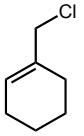
***N*-(2-iodophenyl)cyclohex-1-ene-1-carboxamide (S10):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[115]



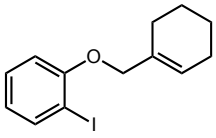
***N*-(2-iodophenyl)-*N*-methylcyclohex-1-ene-1-carboxamide (S11):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[115]



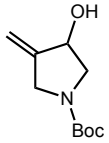
cyclohex-1-en-1-ylmethanol (S12): The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[116]



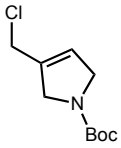
1-(chloromethyl)cyclohex-1-ene (S13): The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[116]



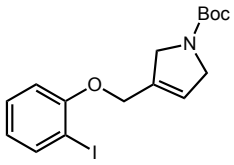
1-(cyclohex-1-en-1-ylmethoxy)-2-iodobenzene (S14): The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported. [117]



***tert*-butyl 3-hydroxy-4-methylenepyrrolidine-1-carboxylate (S15):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[118]



***tert*-butyl 3-(chloromethyl)-2, 5-dihydro-1*H*-pyrrole-1-carboxylate (S16):** The title compound was prepared according to the reported procedure and the NMR data were consistent with those previously reported.[119]

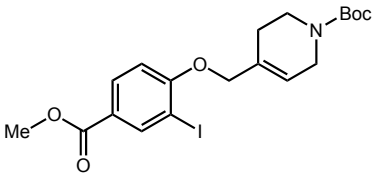


***tert*-butyl 3-((2-iodophenoxy)methyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (S17):** Following general procedure A, the reaction of 2-iodophenol (873 mg, 3.97 mmol, 1.2 equiv), K_2CO_3 (914 mg, 6.62 mmol, 2.0 equiv), *tert*-butyl 3-(chloromethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (720.2 mg, 3.30 mmol, 1.0 equiv), and DMF (33 mL) provided the title compound (682.1 mg, 52% yield) as a clear oil after purification by flash column chromatography (10% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 7.0 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.70 (t, *J* = 6.7 Hz, 1H), 5.87 (d, *J* = 17.8 Hz, 1H), 4.61 (s, 2H), 4.20 (dd, *J* = 18.6, 12.8 Hz, 3H), 4.13 (s, 1H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 156.75, 154.12, 139.50, 134.85, 129.37, 122.92, 122.66, 112.07, 86.49, 79.41, 65.96, 53.32, 52.97, 28.42.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{21}INO_3$: 402.1, found 345.8 (**S17**-*t*Bu)

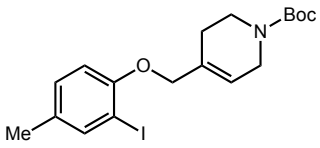


***tert*-butyl-4-((2-iodo-4-(methoxycarbonyl)phenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S18):** Following general procedure B, the reaction of 4-hydroxy-3-iodobenzoate (306 mg, 1.1 mmol, 1.1 equiv), K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv), *tert*-butyl 4- (chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (231.72 mg, 1.0 mmol, 1.0 equiv), and DMF (10 mL) provided the title compound (391 mg, 83% yield) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.8 Hz 1H), 5.84 (s, 1H), 4.50 (s, 2H), 3.93 (s, 2H), 3.85 (s, 3H), 3.53 (s, 2H), 2.21 (s, 2H), 1.44 (s, 9H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.28, 160.36, 154.68, 140.81, 131.38, 131.33, 124.29, 122.67, 121.77, 116.22, 110.98, 85.69, 79.55, 72.01, 51.95, 28.29, 25.58.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{19}H_{25}INO_5$: 474.1, found 417.6 (**S18**-*t*Bu)



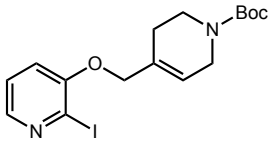
***tert*-butyl 4-((2-iodo-4-methylphenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S19):** Following general procedure B, the reaction of 2-iodo-4-methylphenol (257 mg, 1.1 mmol, 1.1 equiv), K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv), *tert*-butyl 4- (chloromethyl)-3,6-dihydropyridine-

1(2*H*)-carboxylate (231.72 mg, 1.0 mmol, 1.0 equiv), and DMF (10 mL) provided the title compound (359 mg, 84% yield) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 5.84 (s, 1H), 4.41 (s, 2H), 3.94 (s, 2H), 3.55 (s, 2H), 2.24 (m, 5H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.87, 154.72, 139.63, 132.18, 132.08, 129.70, 121.08, 112.16, 86.36, 79.46, 72.05, 43.20, 40.12, 39.28, 28.33, 25.68.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{18}H_{25}INO_3$: 430.1, found 373.7 (**S19**-*t*Bu)

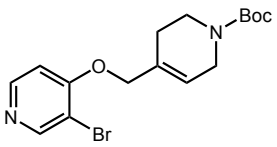


***tert*-butyl 4-(((2-iodopyridin-3-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S20):** Following general procedure B, the reaction of 2-iodopyridin-3-ol (243 mg, 1.1 mmol, 1.1 equiv), K_2CO_3 (304 g, 2.2 mmol, 2.2 equiv), *tert*-butyl 4- (chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (231.72 mg, 1.0 mmol, 1.0 equiv), and DMF (10 mL) provided the title compound (348 mg, 84% yield) as an off-white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.12 (m, 1H), 6.94 (dd, *J* = 8.1, 1H), 5.81 (s, 1H), 4.45 (s, 2H), 3.91 (s, 2H), 3.51 (s, 2H), 2.19 (s, 2H), 1.42 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.83, 154.18, 142.84, 131.36, 123.44, 122.19, 118.30, 112.22, 79.74, 72.16, 43.31, 39.37, 28.48, 25.77.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{22}IN_2O_3$: 417.1, found 416.7

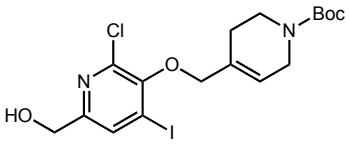


***tert*-butyl 4-(((3-bromopyridin-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S21):** Following general procedure A, the reaction of 3-bromopyridin-4-ol (396.7 mg, 2.28 mmol, 1.2 equiv), K_2CO_3 (525.2 mg, 3.8 mmol, 2.0 equiv), *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (430.4 mg, 1.9 mmol, 1.0 equiv), and DMF (19 mL) provided the title compound (107.2 mg, 15% yield) as a yellow oil after purification by flash column chromatography (20-100% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.36 (d, J = 5.3 Hz, 1H), 6.79 (d, J = 5.7 Hz, 1H), 5.83 (s, 1H), 4.54 (s, 2H), 3.95 (s, 2H), 3.47 (s, 2H), 2.21 (s, 2H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.65, 154.62, 152.36, 149.74, 130.84, 122.00, 110.30, 108.27, 79.63, 71.46, 28.26, 28.15, 27.87, 25.41.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{22}BrN_2O_3$: 369.1, found 369.1

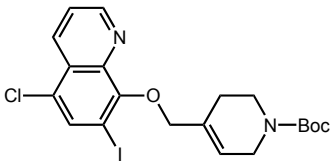


***tert*-butyl 4-(((2-chloro-6-(hydroxymethyl)-4-iodopyridin-3-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S22):** Following general procedure A, the reaction of 2-chloro-6-(hydroxymethyl)-4-iodopyridin-3-ol (236 mg, 0.825 mmol, 1.1 equiv), K_2CO_3 (207 mg, 1.5 mmol, 2.0 equiv), *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (174 mg, 0.75 mmol, 1.0 equiv), and DMF (7.5 mL) provided the title compound (184 mg, 51% yield) as a clear oil after purification by flash column chromatography (20-50% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (t, *J* = 0.7 Hz, 1H), 5.58 (s, 1H), 4.68 (dd, *J* = 5.7, 0.7 Hz, 2H), 4.43 (s, 2H), 3.98 (s, 2H), 3.60 (t, *J* = 5.7 Hz, 2H), 2.66 (t, *J* = 5.7 Hz, 1H), 2.41 (s, 2H), 1.46 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.79, 154.79, 150.46, 143.81, 130.40, 105.13, 80.29, 76.37, 68.92, 62.46, 43.01, 39.27 28.42, 26.29, 25.55.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{23}ClN_2O_4$: 481.0, found 481.0



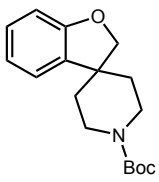
***tert*-butyl 4-(((5-chloro-7-iodoquinolin-8-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S23):** Following general procedure A, the reaction of 5-chloro-7- iodoquinolin-8-ol (336 mg, 1.1 mmol, 1.1 equiv), K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv), *tert*-butyl 4-(chloromethyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (231.72 mg, 1.0 mmol, 1.0 equiv), and DMF (10 mL) provided the title compound (378 mg, 76% yield) as a green oil after purification by flash column chromatography (30% EtOAc/Hex eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (m, 1H), 8.53 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.04 (s, 1H), 7.55 (dd, *J* = 8.6, 4.1 Hz, 1H), 5.87 (s, 1H), 4.83 (s, 2H), 3.92 (s, 2H), 3.61 (s, 2H), 2.59 (s, 2H), 1.46 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.70, 150.22, 142.28, 134.95, 133.33, 132.82, 128.16, 127.32, 126.37, 122.12, 90.08, 79.36, 77.63, 77.04, 43.64, 40.73, 28.33, 26.40.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{20}H_{23}ClIN_2O_3$: 501.0, found 500.5

4.4.4 Procedure and Characterization Data

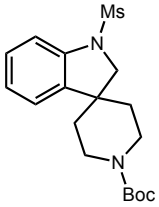


***tert*-butyl 2*H*-spiro[benzofuran-3,4'-piperidine]-1'-carboxylate (1):** Following general procedure C, the reaction of *tert*-butyl 4-((2- iodophenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S5**) (124.5 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (70.3 mg, 81% yield) as an off-white solid after purification by flash chromatography (10-50% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (td, *J* = 7.7, 2.2 Hz, 1H), 7.11 (dd, *J* = 7.5, 2.2 Hz, 1H), 6.89 (td, *J* = 7.5, 2.4 Hz, 1H), 6.82 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.40 (s, 2H), 4.07 (s, 2H), 2.90 (t, *J* = 13.1 Hz, 2H), 1.85 (m, 2H), 1.73 (d, *J* = 13.6 Hz, 2H), 1.49 (d, *J* = 2.6 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.29, 154.77, 134.30, 128.50, 122.90, 120.61, 109.84, 79.77, 79.70, 44.53, 35.16, 28.38.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{24}NO_3$: 290.2, found 233.9 (**1**-*t*Bu)

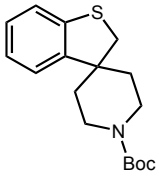


***tert*-butyl 1-(methylsulfonyl)spiro[indoline-3,4'-piperidine]-1'-carboxylate (2):** Following general procedure C, the reaction of *tert*-butyl 4-((*N*-(2-iodophenyl)methylsulfonamido)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S7**) (153 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (89.1 mg, 81% yield) as a yellow solid after purification by flash chromatography (50% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 1H), 7.23 (td, *J* = 7.7, 1.3 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 4.13 (s, 2H), 3.84 (s, 2H), 2.91 (s, 3H), 2.89 – 2.82 (m, 2H), 1.84 (q, *J* = 13.9 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.48 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.72, 140.95, 138.29, 128.82, 123.85, 123.27, 113.36, 79.94, 59.10, 42.97, 36.10, 34.19, 28.45.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{18}H_{27}N_2O_4S$: 367.2, found 311.1(**2**-*t*Bu)

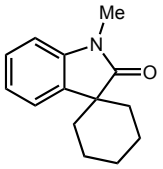


***tert*-butyl 2*H*-spiro[benzo[*b*]thiophene-3,4'-piperidine]-1'-carboxylate (3):** Following general procedure C, the reaction of *tert*-butyl 4-(((2-iodophenyl)thio)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S9**) (129.4 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (33.9 mg, 37% yield) as a yellow oil after purification by preparative TLC (20% EtOAc/Hex eluent).

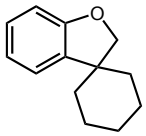
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 1H), 7.14 (td, *J* = 7.7, 7.2, 1.9 Hz, 1H), 7.10 – 7.03 (m, 2H), 4.11 (s, 2H), 3.32 (s, 2H), 2.91 (s, 2H), 1.82 (m, 4H), 1.49 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.75, 148.57, 141.56, 128.40, 125.41, 123.52, 122.49, 79.62, 50.58, 40.81, 36.79, 28.84.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{24}NO_2S$: 306.2, found 251.9 (**3**-*t*Bu)



1'-methylspiro[cyclohexane-1,3'-indolin]-2'-one (8): Following general procedure C, the reaction of *N*-(2-iodophenyl)cyclohex-1-ene-1-carboxamide (**S11**) (102.4 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (32.9 mg, 51% yield) as a yellow solid after purification by flash chromatography (50% EtOAc/Hexanes). The physical properties and spectral data were consistent with the reported values. The NMR data were consistent with those previously reported.[120]

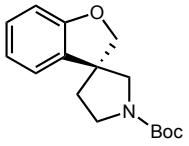


2*H*-spiro[benzofuran-3,1'-cyclohexane] (5): Following general procedure C, the reaction of 1-(cyclohex-1-en-1-ylmethoxy)-2- iodobenzene (**S14**) (94.3 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5.0 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (53.1 mg, 94% yield) as a white solid after purification by flash chromatography (0-10% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15-7.10 (m, 2H), 6.87 (td, *J* = 7.4, 1.0 Hz, 1H), 6.80 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.36 (s, 2H), 1.81 – 1.71 (m, 5H), 1.65 (td, *J* = 13.3, 4.5 Hz, 2H), 1.45-1.28 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 159.23, 136.21, 127.94, 122.82, 120.28, 109.53, 80.90, 46.04, 36.66, 25.36, 23.23.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{13}H_{17}O$: 189.1, found 188.1

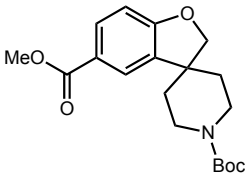


***tert*-butyl (*R*)-2*H*-spiro[benzofuran-3,3'-pyrrolidine]-1'-carboxylate (6):** Following general procedure C, the reaction of *tert*-butyl 3-((2-iodophenoxy)methyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**S17**) (120.4 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5.0 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (56.2 mg, 68% yield) as a yellow oil after purification by flash chromatography (5-50% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$)δ 7.17 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.49-4.28 (m, 2H), 3.74-3.37 (m, 4H), 2.18 (dt, *J* = 17.0, 8.8 Hz, 1H), 2.05 (ddd, *J* = 12.3, 7.4, 4.0 Hz, 1H), 1.48 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) *reported as a mix of rotomers* δ 171.00, 159.80, 154.37, 130.29, 128.89, 122.67, 120.86, 109.82, 81.71, 79.56, 60.26, 56.84, 56.05, 51.54, 51.12, 45.23, 44.91, 38.17, 36.96, 28.37.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{22}NO_3$: 276.2, found 220.1 (**6**-*t*Bu)



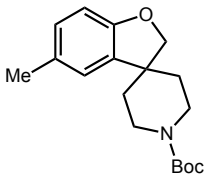
1'-(*tert*-butyl) 5-methyl 2*H*-spiro[benzofuran-3,4'-piperidine]-1',5-dicarboxylate (7): Following general procedure C, the reaction of *tert*-butyl 4-((2-iodo-4-(methoxycarbonyl)phenoxy)methyl)-3,6-dihydropyridine-1(2*H*)- carboxylate (**S18**) (114 mg, 0.24 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.20 mL, 1.2 mmol, 5.0 equiv), and 3DPAFIPN (7.0

mg, 5 mol%) provided the product (64.2 mg, 77% yield) as a light yellow oil after purification by flash chromatography (20% EtOAc/Hex eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 4.46 (s, 2H), 4.08 (s, 2H), 3.85 (s, 3H), 2.87 (d, *J* = 13.5 Hz, 2H), 1.87 (td, *J* = 12.9, 4.6 Hz, 2H), 1.71 (d, *J* = 13.6 Hz, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.65, 163.42, 152.97, 134.75, 131.45, 124.88, 122.93, 114.17, 109.53, 80.80, 79.76, 51.76, 44.17, 35.90, 28.33.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{19}H_{26}NO_5$: 348.2, found 291.8 (**7**-*t*Bu)

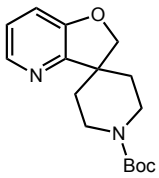


***tert*-butyl 5-methyl-2*H*-spiro[benzofuran-3,4'-piperidine]-1'-carboxylate (8):** Following general procedure C, the reaction of *tert*-butyl 4-((2-iodo-4- methylphenoxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S19**) (129 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5.0 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (59.2 mg, 65% yield) as a yellow oil after purification by flash chromatography (10% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (ddd, *J* = 8.1, 1.9, 0.8 Hz, 1H), 6.91 (dt, *J* = 1.9, 0.7 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 4.37 (s, 2H), 4.07 (s, 2H), 3.15 – 2.73 (m, 2H), 2.29 (s, 3H), 1.89-1.77 (m, 2H), 1.75 – 1.64 (m, 2H), 1.49 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 157.16, 154.70, 134.28, 129.86, 128.84, 123.43, 114.50, 109.32, 79.84, 79.61, 44.54, 35.78, 28.36, 20.76.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{18}H_{26}NO_3$: 304.2, found 248.2 (**8**-*t*Bu)

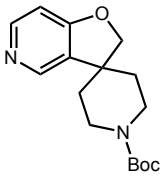


***tert*-butyl 2*H*-spiro[furo[3,2-*b*]pyridine-3,4'-piperidine]-1'-carboxylate (9):** Following general procedure C, the reaction of *tert*-butyl 4-(((2-iodopyridin-3- yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S20**) (125.3 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (73.2 mg, 84% yield) as a yellow solid after purification by flash chromatography (50% EtOAc/Hex eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.6 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 2H), 4.43 (s, 2H), 4.07 (s, 2H), 3.05 (t, *J* = 11.7 Hz, 2H), 2.01 (td, *J* = 12.1, 10.3, 3.6 Hz, 2H), 1.66 (d, *J* = 13.4 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.44, 154.56, 153.06, 141.69, 122.62, 116.08, 80.61, 79.48, 43.66, 40.01 34.38, 28.34.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{23}N_2O_3$: 291.2, found 291.2

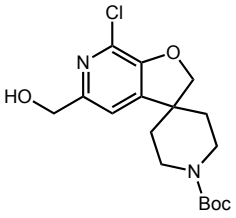


***tert*-butyl 2*H*-spiro[furo[3,2-*c*]pyridine-3,4'-piperidine]-1'-carboxylate (10):** Following general procedure C, the reaction of *tert*-butyl 4-(((3-bromopyridin-4-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S21**) (110.5 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (32.2 mg, 37% yield) as a clear oil after purification by flash chromatography (60-100% EtOAc/Hex eluent).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 2H), 6.71 (d, *J* = 5.5 Hz, 1H), 4.40 (s, 2H), 3.95 (d, *J* = 14.1 Hz, 2H), 2.92 (t, *J* = 12.5 Hz, 2H), 1.82 (ddd, *J* = 13.6, 11.2, 4.5 Hz, 2H), 1.71 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.13, 154.54, 150.20, 144.60, 131.00, 106.07, 81.06, 79.85, 77.05, 43.35, 35.54, 28.26.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{16}H_{23}N_2O_3$: 291.2, found 291.2

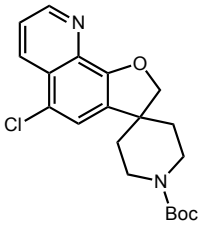


***tert*-butyl 7-chloro-5-(hydroxymethyl)-2*H*-spiro[furo[2,3-*c*]pyridine-3,4'-piperidine]-1'-carboxylate (11):** Following general procedure C, the reaction of *tert*-butyl 4-(((2-chloro-6-(hydroxymethyl)-4-iodopyridin-3-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S22**) (150 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (71.3 mg, 67% yield) as a yellow oil after purification by flash chromatography (20% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (s, 1H), 4.68 (d, *J* = 5.0 Hz, 2H), 4.55 (s, 2H), 4.07 (s, 2H), 2.96 – 2.88 (m, 3H), 1.88-1.80 (m, 2H), 1.79 – 1.72 (m, 2H), 1.48 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.55, 152.82, 151.39, 146.12, 132.91, 131.44, 114.66, 80.89, 80.10, 64.33, 45.97,m40.52, 35.84, 35.24, 28.34.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{17}H_{24}ClN_2O_4$: 355.1, found 355.1



***tert*-butyl 5-chloro-2*H*-spiro[furo[3,2-*h*]quinoline-3,4'-piperidine]-1'-carboxylate (12):**

Following general procedure C, the reaction of *tert*-butyl 4-(((5-chloro-7-iodoquinolin-8-yl)oxy)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**S23**) (150 mg, 0.3 mmol, 1.0 equiv), N,N-diisopropylethylamine (0.26 mL, 1.5 mmol, 5.0 equiv), and 3DPAFIPN (10 mg, 5 mol%) provided the product (42.7 mg, 38% yield) as a brown oil after purification by flash chromatography (10-50% EtOAc/Hex eluent).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.50 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.48 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.39 (s, 1H), 4.71 (s, 2H), 4.15 (s, 2H), 2.89 (s, 2H), 1.93 (m, 2H), 1.82 (d, *J* = 13.4 Hz, 2H), 1.49 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.62, 153.71, 150.29, 136.22, 133.19, 131.75, 126.53, 122.26, 121.88, 121.58, 116.25, 81.08, 79.87, 46.04, 35.94, 28.36.

LRMS (APCI) m/z: $[M+H]^+$ calc'd. for $C_{20}H_{24}ClN_2O_3$: 375.1, found 374.8

4.5 Chapter Four References

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