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Radical Conjugate Addition of Nitrogen Heterocycles and Tertiary Amines

By

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Doctor of Philosophy

Chemistry

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Radical Conjugate Addition of Nitrogen Heterocycles and Tertiary Amines

By

R. Adam Aycock

B.S., University of North Alabama, 2015

Advisor: Nathan T. Jui, Ph.D.

An abstract of

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

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Doctor of Philosophy

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2020

Abstract

Radical Conjugate Addition of Nitrogen Heterocycles and Tertiary Amines

By: R. Adam Aycock

The direct addition of pyridine and diazine units to electron-poor alkenes has been achieved via a redox radical mechanism that is enabled by limiting the effective concentration of the hydrogen-atom source. The described method is tolerant of acidic functional groups and is generally applicable to the union of a wide range of Michael acceptors and 6-membered heterocyclic halides. This technology was advanced to the preparation of a β-heteroaryl α-amino acids by the union of heteroaryl radicals with protected dehydroalanine derivatives. This process was conducted with good efficiency on large scale, the application of these conditions to amino ketone synthesis is shown, and a simple protocol is given for enantioenriched amino acid synthesis from a number of radical precursors. Replacement of terminal reductant, Hantzsch ester, with trialkylamines revealed an unexpected reactive pathway: α-amino radical conjugate addition to dehydroalanine *via* a C–H functionalization mechanism. This protocol, driven by visible light, is highly chemoselective, redox- and proton-neutral, and effectively activates highly complex amine structures for coupling with a range of Dha substrates to furnish unnatural amino acids and peptide conjugates. This mechanistic manifold was advanced to the cyclobutylation of aniline derivatives by the direct addition to electrophilic strain-activated bicyclobutanes.

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Chapter 1

Introduction to Photoredox Catalysis

1.1 Photoredox Catalysis in the Context of Radical Chemistry

Open shell radicals are highly reactive intermediates that have a reputation for being indiscriminate with their reactivity. Although two radical species will react with one another at nearly diffusion-controlled rates, radicals will also react with most other organic compounds, including the solvents in which they are formed. Because radicals are so reactive, the main challenge is not the discovery of new radical reactions, but rather, understanding how to control their reactivity. Traditional methods for the generation of radicals have often required harsh reaction conditions, typically involving elevated temperatures, ultraviolet irradiation, or hazardous radical initiators. Photoredox catalysis has answered many of the major limitations of classical radical chemistry by offering a mechanistic paradigm that operates smoothly under mild conditions and is driven by the most abundant energy source in the universe: light. Consequently, the rate of development of radical-driven synthetic technology has surged over the last 20 years as photoredox catalysis has been established a mature science.[1]

1.2 Photoredox Catalysis

Photoredox catalysis is a catalytic method that harnesses energy from visible light to increase the rate of synthetic transformations via single electron transfer events. Photoredox catalysts are light-sensitive transition metal complexes or organic dyes (illustrated in Figure 1.1) that mediate the conversion of photonic energy to chemical energy and subsequently, the transfer of energy or electrons between molecules. Upon photoirradiation, a ground-state photoredox catalyst (PC)

[1] (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113* (7), 5322–5363. (b) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116* (17), 10075–10166.

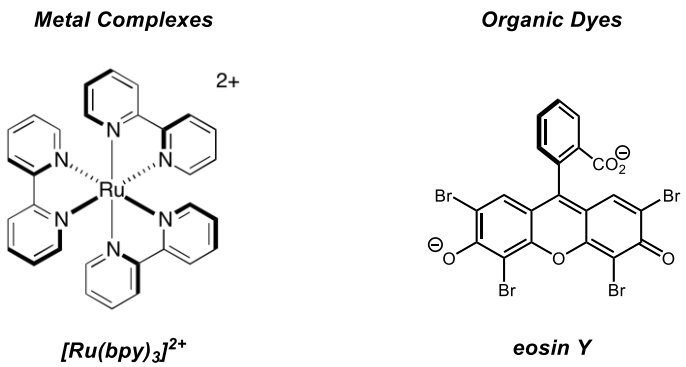

Figure 1.1. Examples of common photoredox catalysts

absorbs a photon, transitioning with high efficiency to an excited state. In the case of a transition metal complex photoredox catalyst (such as $[Ru(bpy)_3]Cl_2$), this occurs when absorption of a photon by the ground state promotes a *d* electron from the t_{2g} orbital of the metal center to the π^* orbital centered on an aromatic ligand to form a singlet excited state (metal-ligand charge transfer, MLCT).[2] From this point, several pathways are possible, as illustrated in Figure 1.2. The complex may relax by radiative decay − a process known as fluorescence. Alternatively, the promoted electron may relax through a process called internal conversion (not shown), in which a small amount of energy is lost to vibrational decay and loss of heat. The system may, instead, undergo intersystem crossing to give a long-lived triplet excited state (T1). Further relaxation of the triplet excited state by radiative decay is a process known as phosphorescence. Because phosphorescence requires a spin-forbidden relaxation, triplet excited states exhibit longer lifetimes than their singlet-

[2] (a) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159. (b) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. *Coord. Chem. Rev.* **1988**, *84*, 85.

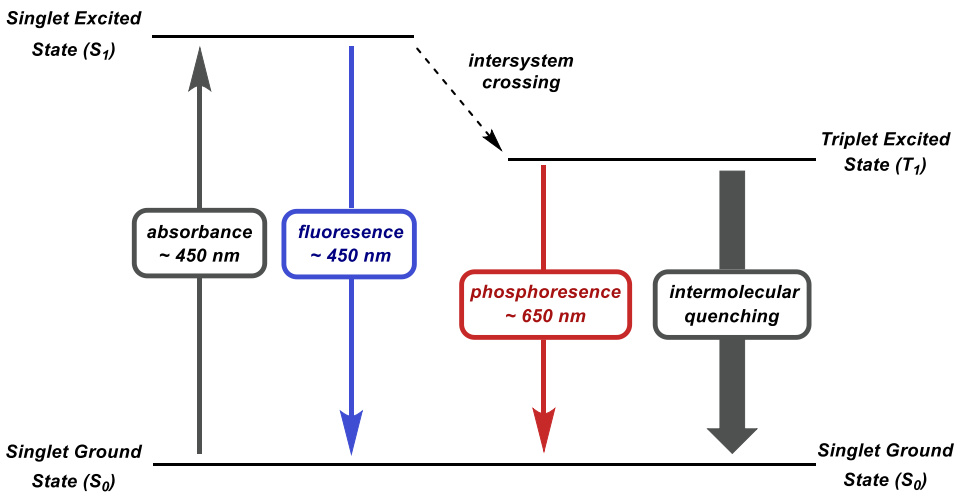

Figure 1.2. Jablonski diagram for excitation, emission, and quenching of a photoexcitable complex

state counterparts. These extended excited state lifetimes (1100 ns for $[Ru(bpy)_3]^{2+}$)[3] are often sufficient for intermolecular energy- or electron-transfer processes to proceed faster than decay to ground state. In addition to the particular catalyst present (and its inherent photophysical and redox properties), the operative pathway in a given photoredox reaction is dictated by the properties of other reactants in the system. The possible catalytic pathways are categorized based on the transfer of energy or electrons, to (or from) an excited state photosensitizer. Energy transfer pathways can be further broken down into Dexter and Förster energy transfer processes. Dexter energy transfer mechanisms operate by transfer of a high-energy electron from the triplet excited state of the photocatalyst (PC*) to the LUMO of an acceptor molecule and a second (concerted or step-wise)

[3] Kalyanasundaram, K. Photophysics, Photochemistry and Solar Energy Conversion with Tris(Bipyridyl)Ruthenium(II) and Its Analogues. *Coord. Chem. Rev.* **1982**, *46* (C), 159–244.

electron transfer from the HOMO of the ground-state acceptor molecule to t_{2g} SOMO of the PC*, giving an excited-state acceptor molecule and returning PC to ground state. Dexter energy transfer pathways are rather unpredictable, and to date, process that operate via this mechanistic paradigm are largely identified by serendipitous discovery. Förster energy transfer processes occur via radiative decay of PC* (emission of photon of longer wavelength than the preceding absorption), followed by absorption of the emitted photon by an acceptor molecule (photoexcitation) present in the system. Consequently, Förster energy transfer processes are substantially more predictable,

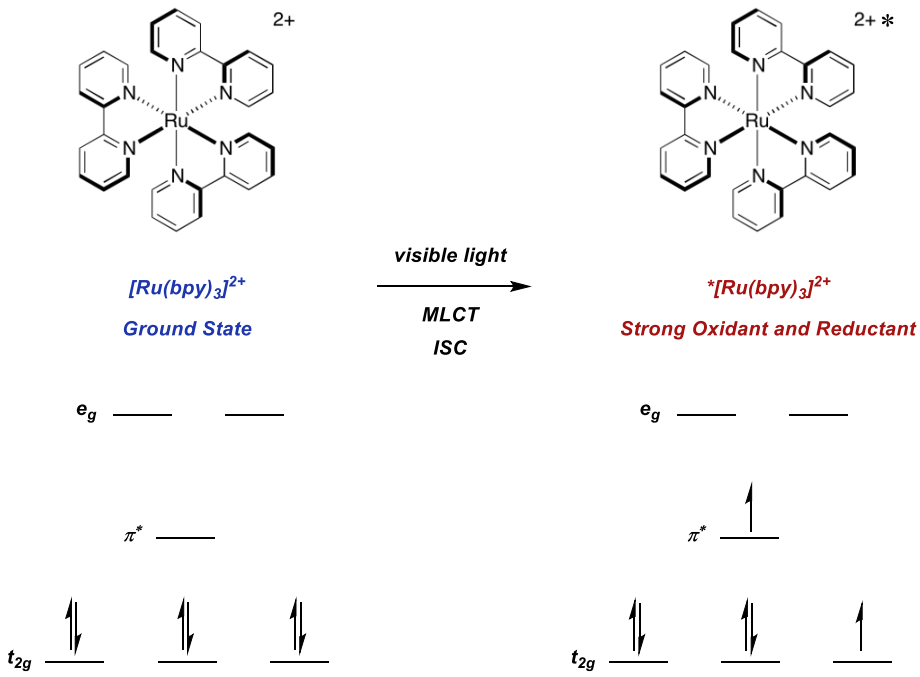

Figure 1.3. Molecular Orbital Diagram of Photoredox Catalyst $[Ru(bpy)_3]^{2+}$.

as the emission and absorption steps that follow excitation of the catalyst can be characterized by fluorimetry. In addition to energy transfer processes, photoredox catalyst are capable of driving reactions via electron-transfer mechanisms that are subcategorized by the redox activity of the photosensitizer following excitation.

In its triplet excited state, a photoredox catalyst has two unpaired electrons, so it is simultaneously a potent reductant and oxidant (Figure 1.3). Consequently, PC* may follow one of two possible redox pathways. If PC* behaves as a reductant, it loses an electron, forming a very

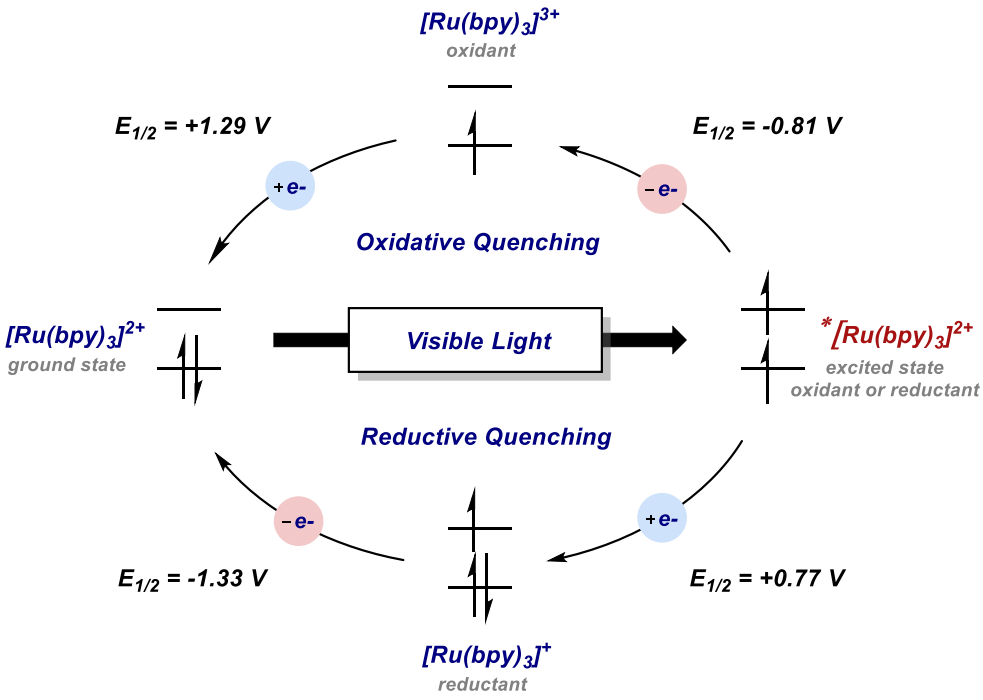

Figure 1.4 Quenching Cycles for $[Ru(bpy)_3]^{2+}$.

potent oxidant, and subsequently gains an electron to return to ground state. Alternatively, PC*can behave as an oxidant, gaining an electron to form a very potent reductant, followed by loss of an electron to return to ground state. The two pathways are known as oxidative and reductive quenching, respectively (Figure 1.4). The ability of the catalyst to behave as both oxidant and reductant in each mechanistic pathway and the ability to perform redox-neutral reactions, enable exotic bond constructions not formed by other catalytic modes. The operable mechanism can be probed by a process commonly known as Stern-Volmer luminescence quenching.[4]

1.3 Probing Photoredox Mechanism

Stern-Volmer luminescence quenching is a spectroscopic technique used to identify the components of a photoredox reaction that participate in single-electron transfer events with the excited state of the photoredox catalyst. These components are termed quenchers because they quench the excited state of the catalyst by donating or accepting an electron. Stern-Volmer luminescence quenching is conducted by irradiating a sample doped with a known amount of quencher with light and measuring luminescence intensity (I). The fraction of the luminescence intensity of a sample containing no quencher (I_0) to I is plotted as a function of the concentration of quencher, and the slope of the line describes the product of quenching rate of a given quencher (k_q) and the concentration of photoredox catalyst (τ_0), as shown in Eq. 1.

Eq. 1. $$\frac{I}{I_0} = k_q \tau_o \qquad (1.1)$$

[4] Lytle, F. E.; Desilets, D. J.; Kissinger, P. T. Improved Method for Determination of Stern-Volmer Quenching Constants. *Anal. Chem.* **1987**, *59* (8), 1244–1246.

This equation can be used to quantify the effectiveness of a given quencher. Compounds for which $k_q\tau_0$ is greater than zero are effective quenchers of the excited state of the photoredox catalyst. Comparison of the redox properties of compounds that are identified as quenchers can aid in the determination of the most plausible mechanistic pathway for a given system.

Although photoredox mechanisms are often visually represented as closed cycles, it is common for systems to operate as radical chain processes. A given system may operate by a closed catalytic cycle, a chain mechanism, or a combination of the two pathways. Two methods are commonly employed to determine if a mechanism exhibits radical chain character: "light/dark" experiments and quantum yield.[5] Light/dark experiments are qualitative analytical methods that enable a rough approximation of the mechanistic pathway. A light/dark experiment is performed by applying a temporal burst of irradiation to a photoredox system to a point of incomplete conversion (t_1), after which the reaction is allowed to proceed without irradiation Reaction progress is analyzed at t_1, and again after a period of time without irradiation (t_2). Reaction progress at t_1 and t_2 are compared, and if additional reaction progress is observed at t_2, it can be concluded that the reaction proceeds (at least in part) via a radical chain mechanism. Quantum yield is a quantitative spectroscopic method by which the number of photons absorbed by a system over a time interval (t) is measured and compared to the product yield of the reaction over the same interval (*t*) in accord with Eq. 2. Specifically, the quantum yield (Φ) can be calculated by the fraction of moles of product to the product of photon flux (in einstein s^{-1}), time of irradiation (t), and fraction of light absorbed by the system (*f*).

$$\text{Eq. 2.} \quad \Phi = \frac{mol\ product}{flux \cdot t \cdot f} \qquad (1.2)$$

[5] Cismesia, M. A.; Yoon, T. P. Characterizing Chain Processes in Visible Light Photoredox Catalysis. *Chem. Sci.* **2015**, *6* (10), 5426–5434.

Quantum yield (*Φ)* describes the fraction of moles of product to moles of photons absorbed by the system (assuming luminescence quenching fraction = 1), so if $\Phi = 1$, then one mole of product is formed per mole of light that is absorbed, which indicates that exactly one catalytic turnover occurs per absorbed photon. When $\Phi = 1$, the system operates via a closed-loop catalytic cycle; however, if $\Phi > 1$, then the system operates, at least partially, via a radical chain mechanism. If $\Phi >> 1$, then it can be concluded that a system operates predominantly via radical chain mechanism. A more accurate description of average chain length can be calculated as a fraction of Φ to luminescence quenching fraction (Q), which can be obtained from Stern-Volmer luminescence quenching (Eq. 3.).

Eq. 3. $chain\ length = \frac{\Phi}{Q}$,where $Q = \frac{k_q}{\tau_0^{-1} + k_q}$ (1.3)

1.4 Synthetic Utility of Photoredox Catalysis

One of the earliest reports of photoredox catalysis used in a synthetic fashion was Kellog's 1978 report of sulfonium ion reduction to corresponding alkanes or thioethers. This protocol employed $[Ru(bpy)_3]^{2-}$ and dihydropyridines as stoichiometric reductant.[6] Shortly after Fukuzumi and Tanaka[7] and Pac[8] developed reported related systems applicable to the reduction of electron-deficient olefins, aromatic ketones, and benzylic and phenacyl halides. The first net oxidative photoredox-catalyzed reaction was discolosed by Cano-Yelo and Deronzier in 1984 – a process

[6] (a) Hedstrand, D. M.; Kruizinga, W. M.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, *19*, 1255−1258. (b) van Bergen, T. J.; Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *J. Org. Chem.* **1979**, *44*, 4953−4962.

[7] (a) Hironaka, K.; Fukuzumi, S.; Tanaka, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1705−1709. (b) Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. *J. Am. Chem. Soc.* **1987**, *109*, 305−316. (c) Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *J. Phys. Chem.* **1990**, *94*, 722−726.

[8] (a) Pac, C.; Ihama, M.; Yasuda, M.; Miyauchi, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 6495−6497. (b) Pac, C.; Miyauchi, Y.; Ishitani, O.; Ihama, M.; Yasuda, M.; Sakurai, H. *J. Org. Chem.* **1984**, *49*, 26−34. (c) Ishitani, O.; Ihama, M.; Miyauchi, Y.; Pac, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1527−1531. (d) Ishitani, O.; Pac, C.; Sakurai, H. *J. Org. Chem.* **1983**, *48*, 2941−2942. (e) Ishitani, O.; Yanagida, S.; Takamuku, S.; Pac, C. *J. Org. Chem.* **1987**, *52*, 2790−2796.

that results in the oxidation of benzylic alcohols the corresponding benzaldehyde, employing arenediazonium salts as stoichiometric oxidant.[9] Soon after, Cano-Yelo and Deronzier also disclosed the first redox-neutral photoredox-catalyzed synthetic transformation, in which phenanthrenes were prepared via a $[Ru(bpy)_3]^{2-}$ catalyzed Pschorr reaction.[10]

Although the origins of photoredox catalysis can be traced back to the 1950s (and the origin of synthetic application to the late 1970s) the birth of the field is widely viewed as the concurrent publications of MacMillan and Yoon in 2008. MacMillan[11] reported the α-alkylation of aldehydes, accomplished through a combination of photoredox and enamine organocatalysis, and Yoon[12] disclosed a photoredox-catalyzed intramolecular [2+2] cycloaddition of two enones (using sunlight as irradiation source). Since these seminal reports, the field of photoredox catalysis has become widely adopted by the synthetic community, breathing new life into radical chemistry.[13]

[9] Cano-Yelo, H.; Deronzier, A. *Tetrahedron Lett*. **1984**, *25*, 5517−5520.
[10] (a) Cano-Yelo, H.; Deronzier, A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1093−1098. (b) Cano-Yelo, H.; Deronzier, A. *J. Photochem*. **1987**, *37*, 315−321.
[11] Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77−80.
[12] Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc*. **2008**, *130*, 12886−12887.
[13] (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nature Chem.* **2010**, *2*, 527. (b) Narayanam, J. M. R.; Stephenson, C. R. *J. Chem. Soc. Rev.* **2011**, *40*, 102. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (e) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116* (17), 10075–10166.

Chapter 2

A mild catalytic system for radical conjugate addition of nitrogen heterocycles

Adapted from: R. A. Aycock, H. Wang, and N. T. Jui. A mild catalytic system for radical conjugate addition of nitrogen heterocycles. *Chem. Sci.* **2017**, 8, 3121-3125.

H. Wang contributed to the discovery of optimal conditions for the process described herein. He is also responsible for the scope of halogenated heterocycles and the radical clock experiment. H. Wang also developed the alternate set of conditions using sodium formate as stoichiometric reductant.

2.1 Abstract

The direct addition of pyridine and diazine units to electron-poor alkenes has been achieved via a redox radical mechanism that is enabled by limiting the effective concentration of the hydrogen-atom source. The described method is tolerant of acidic functional groups and is generally applicable to the union of a wide range of Michael acceptors and 6-membered heterocyclic halides.

2.2 Introduction

Pyridines and diazines are critical structural elements in many biologically active small molecules[14] and, as a result, significant research effort has been devoted to their preparation.[15] In addition to de novo heterocycle assembly, a number of powerful methods exist for the functionalization of these heteroarenes. For example, Minisci radical addition is a direct and effective synthetic approach to the preparation of alkyl pyridines and diazines,[16] however, the regiochemical outcome of these processes is largely dictated by the inherent reactivity of a given substrate (or substrate class).[17,18] Catalytic coupling processes of halogenated heteroarene substrates with alkyl metals[19] and, more recently, alkyl halides[20] have been developed for the direct

[14] Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257–10274

[15] Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Blackwell Publishsing Ltd, **2010**

[16] Minisci, F.; Vismara, E.; Fontana, F. Recent Developments of Free-Radical Substitutions of Heteroaromatic Bases. *Heterocycles* **1989**, *28* (1), 489–519

[17] O'Hara, F.; Blackmond, D. G.; Baran, P. S. Radical-Based Regioselective C-H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. *J. Am. Chem. Soc.* **2013**, *135* (32), 12122–12134

[18] Minisci, F.; Vismara, E.; Fontana, F. Recent Developments of Free-Radical Substitutions of Heteroaromatic Bases. *Heterocycles* **1989**, *28* (1), 489–519

[19] (a) Meijere, A. De; Diederich, F. *Edited by Related Titles from Wiley-VCH Handbook of Metathesis Multimetallic Catalysts in Organic Synthesis Modern Aldol Reactions Transition Metals for Organic Synthesis*; 2004; Vol. 1 (b) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd , Ni , Fe) -Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. **2011**, 1417–1492

[20] (a) Everson, D. A.; Buonomo, J. A.; Weix, D. J. Nickel-Catalyzed Cross-Electrophile Coupling of 2-Chloropyridines with Alkyl Bromides Letter. **2013**, 233–238 (b) Krasovskiy, A.; Thomé, I.; Graff, J.; Krasovskaya, V.; Konopelski, P.; Duplais, C.; Lipshutz, B. H. Cross-Couplings of Alkyl Halides with Heteroaromatic Halides , in Water at Room Temperature. *Tetrahedron Lett.* **2011**, *52* (17), 2203–2205 (c) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. An Improved System for the Aqueous Lipshutz-Negishi Cross-Coupling of Alkyl Halides with Aryl Electrophiles. *Angew. Chemie* **2016**, *128* (5), 1881–1885 (d) Wang, S.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Coupling of Aryl Halides with Secondary Alkyl Bromides and Allylic Acetate. *Org. Lett.* **2012**, *14* (13), 3352–3355 (e) Duan, Z.; Li, W.; Lei, A. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Bromides with Alkyl Bromides: Et_3N as the Terminal Reductant. *Org. Lett.* **2016**, *18* (16), 4012–4015 (f) Zhang, P.; Le, C. C.; MacMillan, D. W. C. Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem.*

synthesis of alkylated heteroaromatics. We recently became interested in developing an alternative approach to complex pyridine and diazine synthesis via direct union of these heteroaromatic units with alkenes. More specifically, we envision a general strategy for programmed, regiospecific heteroarene activation that functions through heteroaryl radical intermediates. In contrast to alkyl radicals, aryl radical species effectively engage a wide range of unsaturated substrates.[21] Consequently, mild conditions that

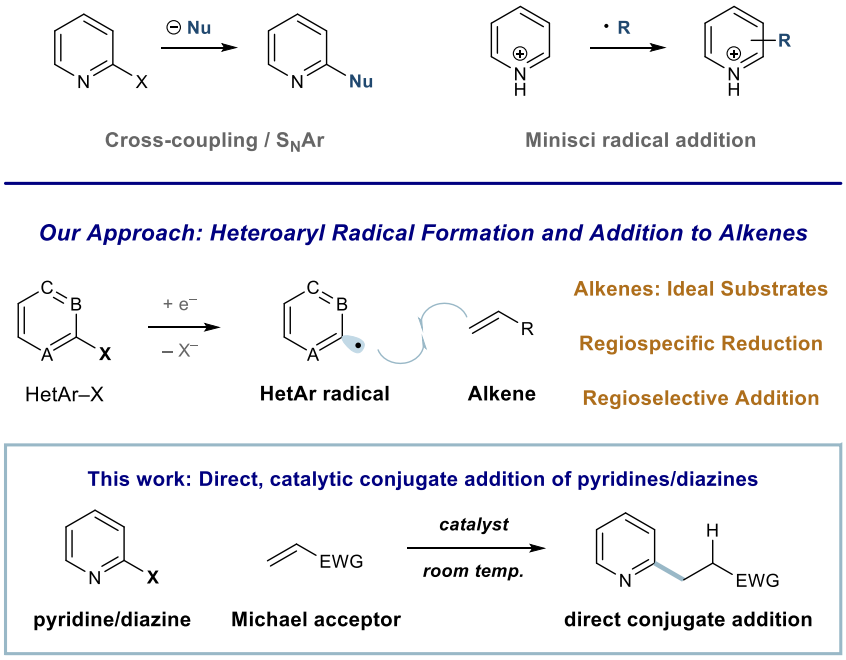

Figure 2.1: General strategies for the synthesis of complex heteroarenes

Soc. **2016**, *138* (26), 8084–8087 (g) Molander, G. A.; Traister, K. M.; ONeill, B. T. Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides. *J. Org. Chem.* **2014**, *79* (12), 5771–5780 (h) Kadunce, N. T.; Reisman, S. E. Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Heteroaryl Iodides and α-Chloronitriles. *J. Am. Chem. Soc.* **2015**, *137* (33), 10480–10483

[21] For recent review of intermolecular addition to alkenes, see: (a) Heinrich, M. R. Intermolecular Olefin Functionalisation Involving Aryl Radicals Generated from Arenediazonium Salts. *Chem. - A Eur. J.* **2009**, *15* (4), 820–833 (b) Fehler, S. K.; Heinrich, M. R. How the Structural Elucidation of the Natural Product Stephanosporin Led to New Developments in Aryl Radical and Medicinal Chemistry. *Synlett* **2015**, *26* (5), 580–603

deliver these reactive intermediates could enable the development of many discrete, practical processes for complex pyridine and diazine synthesis (Fig. 2.1). Here, we describe the development of a catalytic system for heteroaryl radical formation and direct coupling with electron-deficient alkenes, a reductive Meerwein arylation[22] process (illustrated in Fig. 2.1). Conjugate addition is a highly utilized strategic disconnection, but direct Michael addition of 6-membered nitrogen heterocycles remains challenging.

Because pyridines are weakly nucleophilic, they require activation to effectively add to alkenes. Miyaura demonstrated that rhodium-catalyzed asymmetric conjugate addition of o-methoxy pyridylboronic acids is efficient, but analogous coupling of the parent 2-pyridyl boronic acid (devoid of the electron-donating blocking group) was unsuccessful.[23] A 2-pyridylboronate substrate was utilized in Akita's aryl radical conjugate addition system, based on photoredox arylboronate oxidation, to give the alkylpyridine in low yield (24%).[24] Nilsson described an effective system for pyridylcuprate Michael addition,[25] but Gilman reagents are extremely acid-sensitive, which limits their utility in complex molecule synthesis. Additionally, none of these strategies have demonstrated the ability to accomplish diazine conjugate addition. Condon described a Ni-catalyzed reductive Heck process of heteroaryl halides using electrochemistry, but this system was limited to monosubstituted alkenes.[26] Our strategy for heteroarene activation is based on single-electron reduction and fragmentation of heteroaryl halides to regiospecifically

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[24] Yasu, Y.; Koike, T.; Akita, M. Visible Light-Induced Selective Generation of Radicals from Organoborates by Photoredox Catalysis. *Adv. Synth. Catal.* **2012**, *354* (18), 3414–3420
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[26] Condon, S.; Dupré, D.; Lachaise, I.; Nédélec, J. Y. Nickel Catalyzed Electrochemical Heteroarylation of Activated Olefins. *Synthesis (Stuttg).* **2002**, *12*, 1752–1758

afford the corresponding radical species.[27] Aryl radical addition to electron-poor alkenes is facile,[28] and this would offer a general alternative to pyridine and diazine conjugate addition that operates at room temperature and is tolerant of acidic functional groups.

Aryl radicals are indispensable intermediates in organic synthesis, and redox processes of arenediazonium salts [8,9,29] or arylboronic acids[30] are reliable methods for their formation. However, these strategies are limited in the context of pyridine or diazine-based radical generation, due to the instability of the requisite heteroaryl-diazonium[31a] or -boronic acid reagents.[18b] Tin-mediated halogen abstraction delivers (hetero)aryl radical intermediates[32] but intermolecular alkene coupling reactions are challenging within this manifold because hydrogen atom transfer (HAT) to aryl radicals by tin-hydrides is rapid.[33] Our method for reductive aryl radical generation involves photoinduced electron transfer. This mode of radical formation, first described by Beckwith,[34] has

[27] (a) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; Saveant, J. M. Heterogeneous and Homogeneous Electron Transfers to Aromatic Halides. An Electrochemical Redox Catalysis Study in the Halobenzene and Halopyridine Series. *J. Am. Chem. Soc.* **1979**, *101* (13), 3431–3441 (b) Enemærke, R. J.; Christensen, T. B.; Jensen, H.; Daasbjerg, K. Application of a New Kinetic Method in the Investigation of Cleavage Reactions of Haloaromatic Radical Anions. *J. Chem. Soc. Perkin Trans. 2* **2001**, *9*, 1620–1630

[28] (a) Srikanth, G. S. C.; Castle, S. L. Advances in Radical Conjugate Additions. *Tetrahedron* **2005**, *61* (44), 10377–10441 (b) Sibi, M. P.; Manyem, S.; Zimmerman, J. Enantioselective Radical Processes. *Chem. Rev.* **2003**, *103* (8), 3263–3295 (c) Renaud, P.; Gerster, M. Free Radical Reactions Lewis Acids Complexation Chelation Catalysis Use of Lewis Acids in Free Radical Reactions. *Angew. Chem. Int. Ed.* **1998**, *37*, 2562–2579

[29] (a) Galli, C. Radical Reactions of Arenediazonium Ions: An Easy Entry into the Chemistry of the Aryl Radical. *Chem. Rev.* **1988**, *88* (5), 765–792 (b) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; König, B. Visible Light Mediated Photoredox Catalytic Arylation Reactions. *Acc. Chem. Res.* **2016**, *49* (8), 1566–1577 (c) Hari, D. P.; König, B. The Photocatalyzed Meerwein Arylation: Classic Reaction of Aryl Diazonium Salts in a New Light. *Angew. Chemie - Int. Ed.* **2013**, *52* (18), 4734–4743

[30] (a) Bonin, H.; Sauthier, M.; Felpin, F. X. Transition Metal-Mediated Direct C-H Arylation of Heteroarenes Involving Aryl Radicals. *Adv. Synth. Catal.* **2014**, *356* (4), 645–671 (b) Yan, G.; Yang, M.; Wu, X. Synthetic Applications of Arylboronic Acid via an Aryl Radical Transfer Pathway. *Org. Biomol. Chem.* **2013**, *11* (46), 7999–8008 (c) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. Direct C-H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132* (38), 13194–13196

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[32] (a) Curran, D. P.; Jasperse, C. P.; Totleben, M. J. Approximate Absolute Rate Constants for the Reactions of Tributyltin Radicals with Aryl and Vinyl Halides. *J. Org. Chem.* **1991**, *56* (25), 7169–7172 (b) Mirizzi, D.; Hilton, S. T.; Jones, K. Heteroaryl Radicals Review. In *Advances in Heterocyclic Chemistry*; Elsevier, 2010; Vol. 100, pp 101–143

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been recently employed by Stephenson,[35] Read de Alaniz and Hawker,[36] Weaver,[37] and König[38] to accomplish hydrodehalogenation and a range of C–C bond formations, mediated by photoredox catalysts.[39] Notably, Weaver detailed conditions for the reductive coupling of simple alkenes with 2-haloazoles, polyfluorinated (hetero)aromatics, and a single example of an electron-deficient pyrimidine.[24] The successful translation of this radical strategy to heteroaryl conjugate addition could streamline the invention of bioactive small molecules

2.3 Results and discussion

To assess the feasibility of our design, we studied the radical coupling of 2-iodopyridine (1) with the alkylidene malonate 2 (3.0 equivalents). We found that 1 mol% of the iridium-based photoredox catalyst $Ir[dF(CF_3)ppy]_2dtbbpy \cdot PF_6$ (among others)[40] is capable of reductive 2-pyridyl radical formation under irradiation with a commercially available blue LED.

[35] (a) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. Engaging Unactivated Alkyl, Alkenyl and Aryl Iodides in Visible-Light-Mediated Free Radical Reactions. *Nat. Chem.* **2012**, *4* (10), 854–859. (b) Devery, J. J.; Nguyen, J. D.; Dai, C.; Stephenson, C. R. J. Light-Mediated Reductive Debromination of Unactivated Alkyl and Aryl Bromides. *ACS Catal.* **2016**, *6* (9), 5962–5967.

[36] (a) Poelma, S. O.; Burnett, G. L.; Discekici, E. H.; Mattson, K. M.; Treat, N. J.; Luo, Y.; Hudson, Z. M.; Shankel, S. L.; Clark, P. G.; Kramer, J. W.; Hawker, C. J.; Read De Alaniz, J. Chemoselective Radical Dehalogenation and C-C Bond Formation on Aryl Halide Substrates Using Organic Photoredox Catalysts. *J. Org. Chem.* **2016**, *81* (16), 7155–7160. (b) Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; De Alaniz, J. R. A Highly Reducing Metal-Free Photoredox Catalyst: Design and Application in Radical Dehalogenations. *Chem. Commun.* **2015**, *51* (58), 11705–11708.

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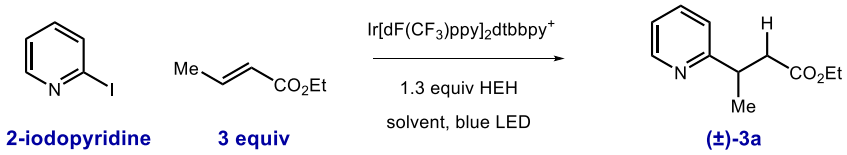
[38] (a) Ghosh, I.; König, B. Chromoselective Photocatalysis: Controlled Bond Activation through Light-Color Regulation of Redox Potentials. *Angew. Chemie - Int. Ed.* **2016**, *55* (27), 7676–7679. (b) Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B. Reduction of Aryl Halides by Consecutive Visible Light-Induced Electron Transfer Processes. *Science.* **2014**, *346* (6210), 725–728. (c) Marzo, L.; Ghosh, I.; Esteban, F.; König, B. Metal-Free Photocatalyzed Cross Coupling of Bromoheteroarenes with Pyrroles. *ACS Catal.* **2016**, *6* (10), 6780–6784.

[39] (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113* (7), 5322–5363. (b) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116* (17), 10075–10166. (c) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40* (1), 102–113.

[40] See experimental section

Alkylamines are effective stoichiometric reductants in photoredox processes, and their use in this context afforded the desired radical conjugate addition (RCA) product 3, albeit in low yield (Table 2.1, entries 1 and 2). While tributylammonium formate (the reductant used by Weaver for 2-bromoazole radical formation,24a–c entry 3) was similar in efficiency to the free base, the use of Hantzsch ester (HEH) delivered 3 in 50% yield (entry 4). In this system, HEH presumably donates an H-atom (to the intermediate radical adduct) and an electron to maintain redox neutrality. We found that the yield of this process was uniformly improved when aqueous solvent mixtures were employed (entries 5–8), and the use of 25% (v/v) H_2O/DMSO afforded the desired product in 96% yield (entry 8).

Table 2.1. Optimization of conditions for heteroaryl radical conjugate addition



2-iodopyridine | 3 equiv | (±)-3a

entry	Photocatalyst	solvent	% yield
1	i-Pr_2Net	CH_3CN	12%
2	NBu_3	CH_3CN	29%
3	$NBu_3 \cdot HCO_2H$	CH_3CN	28%
4	Hantzsch ester	CH_3CN	50%
5	Hantzsch ester	25% H_2O/CH_3CN	80%
6	Hantzsch ester	25% H_2O/DMF	75%
7	Hantzsch ester	25% H_2O/MeOH	78%
8	Hantzsch ester	25% H_2O/DMSO	96%

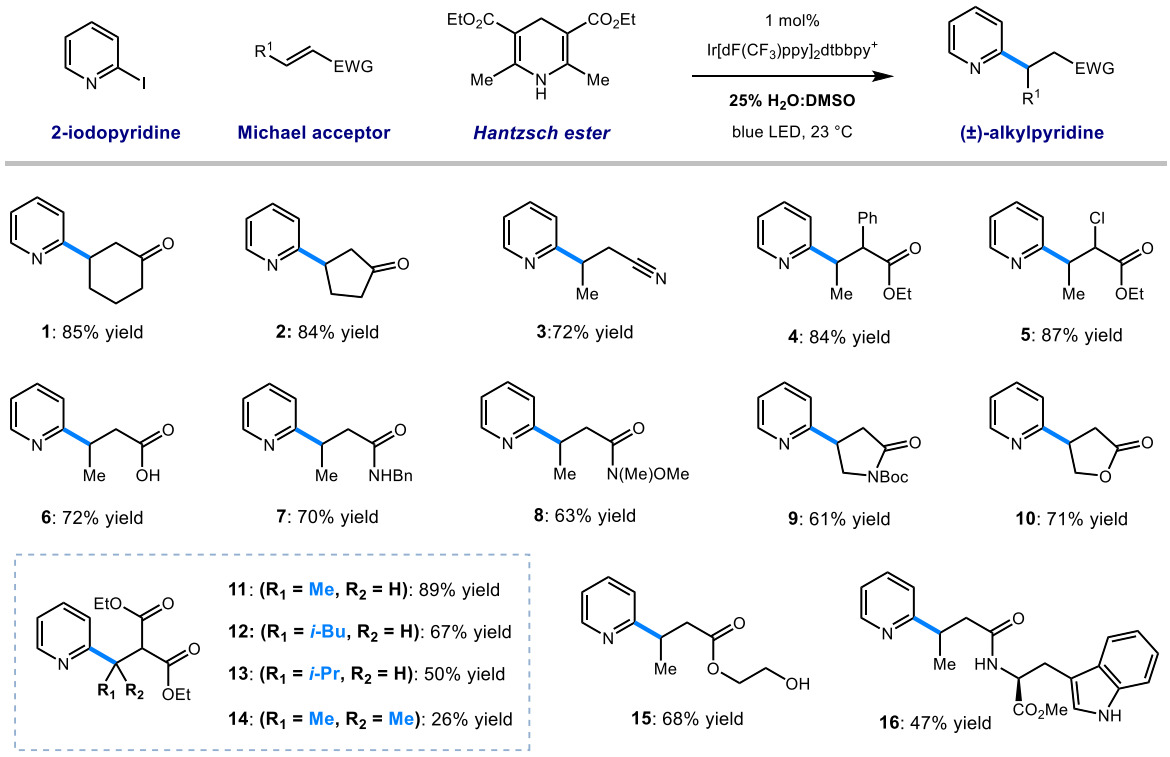
Reaction conditions: 2-iodopyridine (1.0 equiv), dimethyl ethylidene malonate (3.0 equiv), $Ir[dF(CF_3)ppy]_2dtbbpy \cdot PF_6$ (1.0 mol%), amine (1.3 equiv), 25% H_2O/DMSO (10 mL $mmol^{-1}$ heteroarene), blue light, 23 °C, 18 h; Yields determined by GC using dodecane as internal standard.

The scope of this heteroarene conjugate addition protocol was then investigated. As shown in Table 2.2, these mild redox conditions enable the union of 2-pyridyl radical with an array of Michael acceptors with good efficiency. Cyclic ketones and crotononitrile react to give the corresponding pyridines in good yield (entries 1–3, 72–85% yield). Enoates with α-phenyl or α-chloro substitution are effective radical acceptors in this system (entries 4 and 5, 84% yield), giving rise to the complex esters in 4:3 and 4:1 dr, respectively. These radical conditions tolerate N–H and O–H bonds, as exemplified by the effective coupling of carboxylic acid, benzyl amide, and primary alcohol containing substrates (entries 6, 7, 15; 68–74% yield). Steric congestion on the olefin currently diminishes reactivity in this protocol, as demonstrated by entries 11–14; β-methyl, -isobutyl, -isopropyl, and β, β-dimethyl substitution results in formation of the desired malonate products in decreasing order (89%, 67%, 50%, and 26% yield respectively). A tryptophan-derived crotonamide was reacted with pyridyl radical to give the radical conjugate addition product in moderate yield (entry 16, 42% yield) as a 1:1 mixture of diastereomers. Although pyridine derivatives (like the products shown here) are effective radical traps, these conditions select for radical alkene addition. Additionally, phenyl rings (entries 4 and 7) and the indole function in the tryptophan product (entry 16) are unreactive toward aryl radical addition in this system.

We then evaluated the ability of our system to perform radical conjugate addition of other halogenated pyridines and diazines to ethyl crotonate (5 equivalents). Under standard conditions, a number of stable, commercially available heteroaryl iodides and bromides similarly function as radical precursors. As shown in Table 2.3, methyl substitution is tolerated at all positions of 2-pyridyl halides, and the corresponding products were formed in good yield (entries 1–4, 53–82%). Also competent are 3- and 4-iodopyridines (entries 5 and 6), and their use in this system provided

the products in 52% and 48% yield, respectively.[41] Because reductive radical formation is a regiospecific process, this approach allows for the predictable formation of alkylheterocycles as single regioisomers, including 3-alkylpyridines, which are not generally accessible via Minisci radical processes. Phenyl- and chloro substitution is well tolerated to give the corresponding alkylpyridines in useful yield (entries 8, 10, 13; 53–61% yield).

Table 2.2. Heteroaryl radical conjugate addition: scope of the alkene coupling partner



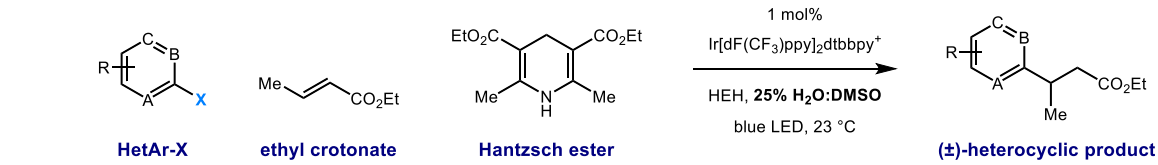
Reaction conditions: 2-iodopyridine (1.0 equiv.), Michael acceptor (3.0 equiv.), Ir[dF(CF3)ppy]2dtbbpy·PF6 (1.0 mol%), Hantzsch ester (1.3 equiv.), 25% H2O/DMSO (10 mL mmol^{-1} heteroarene), blue light, 23 °C, 18 h 4:3 diastereomeric ratio (d.r.)

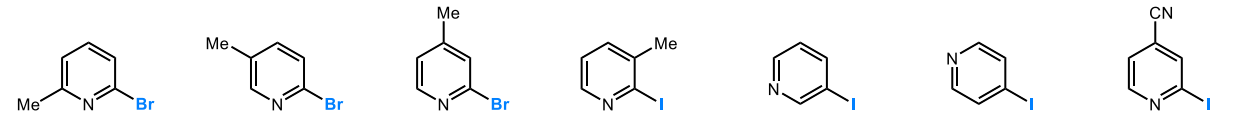
[41] Reduced heteroarene (*via* hydrodehalogenation) was the major byproduct in cases where lower yields of the desired product were obtained

Iodopyridines with the electron-withdrawing nitrile (entry 7) and trifluoromethyl (entry 12) groups were coupled with ethyl crotonate to give the corresponding products in 52% and 68% yield, respectively. Iodopyridines containing Boc-protected amine (entry 9) and benzyl alcohol (entry 11) functions were successfully coupled under these conditions without protecting groups that would be required to participate in anionic conjugate addition protocols (48% and 74% yield), respectively. Importantly, substituted iodopyrimidines also undergo radical formation and conjugate addition in moderate to good yield (entries 16–18, 68–76% yield). However, when iodopyrazine and 2-bromopyrimidine were used, the desired product was formed in trace amounts and a low mass balance was observed. We identified an alternate set of conditions involving the use of sodium formate (3.0 equiv.) and 2,4,6-trimethylaniline (1.0 equiv.) in DMSO solvent, which accomplished the radical conjugate addition of the parent pyrimidine (entry 15) and pyrazine (entry 19) elements in moderate yields (39% and 52%, respectively). While these alternate (sodium formate, trimethylaniline) conditions were effective in some cases, the use of Hantzsch ester as terminal reductant/hydrogen-atom source under aqueous conditions was more generally applicable. Finally, 2-iodopyrazine and 4-bromoazaindole were capable RCA substrates and the corresponding products were delivered in reasonable yield (entries 19 and 20, 52% and 53% yield, respectively). Throughout the course of this study, we observed that the described aqueous reaction conditions are uniquely effective for heteroaryl radical conjugate addition. Indeed, the use of aqueous solvents has improved the efficiency of other radical processes.[42] In this system, we noticed that the introduction of water cosolvent resulted in heterogeneous reaction mixtures that became homogeneous with reaction progress. The solubility of HEH decreases precipitously with

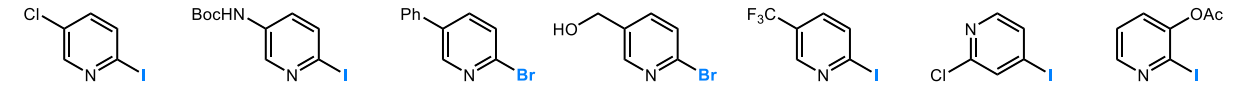
[42] Yorimitsu, H.; Shinokubo, H.; Oshima, K. Synthetic Radical Reactions in Aqueous Media. *Synlett* **2002**, *5*, 674–686

Table 2.3. Heteroaryl radical conjugate addition: Scope of Halogenated Heterocycles[a]

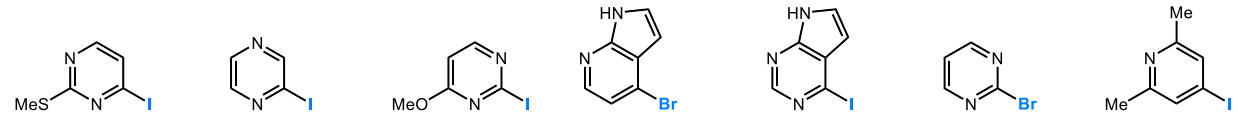




1: 76% yield | **2**: 62% yield | **3**: 82% yield[b] | **4**: 53% yield | **5**: 52% yield | **6**: 48% yield | **7**: 52% yield[c]



8: 58% yield | **9**: 48% yield | **10**: 61% yield | **11**: 74% yield[d] | **12**: 68% yield | **13**: 53% yield | **14**: 58% yield

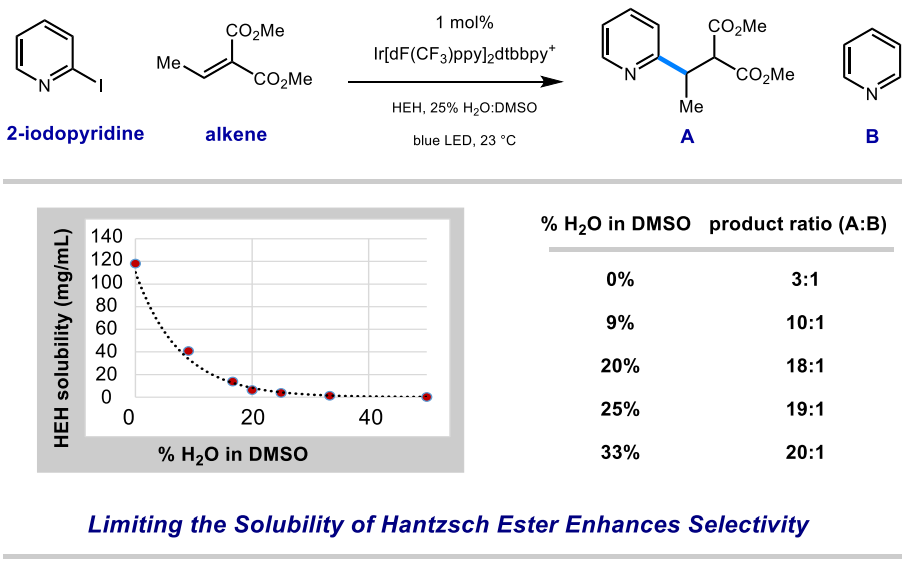


15: 68% yield | **16**: 52% yield[c] | **17**: 68% yield | **18**: 53% yield | **19**: 76% yield | **20**: 39% yield[c] | **21**: 53% yield[d]

[a]Reaction conditions: Halogenated heteroarene (1.0 equiv), ethyl crotonate (5.0 equiv), Ir[dF(CF$_3$)ppy]$_2$dtbbpy•PF$_6$ (1.0 mol%), Hantzsch ester (1.3 equiv), 25% H2O/DMSO (10 mL/mmol heteroarene), blue light, 23 °C, 18 h. [b]2.0 mol% Ir[dF(CF$_3$)ppy]$_2$dtbbpy•PF$_6$. [c]Reaction conditions:Heteroarene (1.0 equiv), ethyl crotonate (3.0 equiv), Ir[dF(CF$_3$)ppy]$_2$dtbbpy•PF$_6$ (1.0 mol%), sodium formate (3.0 equiv), 2,4,6trimethylaniline (1.0 equiv) DMSO (10 mL/mmol heteroarene), blue light, 23 °C, 18 h. [d]Ir(ppy)$_2$dtbbpy•PF$_6$ (1.0 mol%) was used.

increasing amounts of water (shown in Scheme 2.1), and the selectivity for RCA vs. reduction is inversely proportional to HEH solubility (effective concentration), a principle first described by Stork.[43] With the model 2-iodopyridine/ethylidene malonate coupling, the use of 33% (v/v) H_2O/DMSO essentially eliminates the undesired hydrodehalogenation process, giving 20 : 1 selectivity (RCA product A : pyridine B).

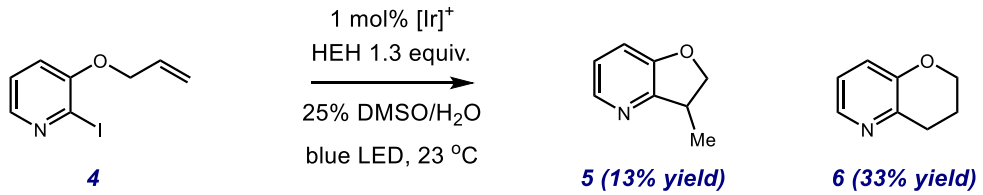
[43] Stork, G.; Sher, P. M. A Catalytic Tin System for Trapping of Radicals from Cyclization Reactions. Regio- and Stereocontrolled Formation of Two Adjacent Chiral Centers. *J. Am. Chem. Soc.* **1986**, *108* (2), 303–304



Scheme 2.1. Limiting reductant (Hantzsch ester) solubility improves selectivity

To further exemplify the intermediacy of heteroaryl radical species in this system, we constructed the allyloxy iodopyridine 4, understanding that reductive pyridyl radical formation would result in intramolecular addition to the pendant alkene. Under standard conditions, 4 underwent activation and radical cyclization to afford a mixture of bicyclic products (46% total yield, shown in scheme 2.1). In addition to the expected product 5 (arising from 5-exo-trig cyclization), we observed preferential (2.5 : 1) formation of the 6-endo product 6,[44] and these data are consistent with the proposed radical nature of the described processes.

[44] While radical cyclization typically occurs predominantly or exclusively via the 5-exo mode, aryl radical cyclizations can afford mixtures of exo and endo products. In these processes, endo products can arise from two different pathways: direct 6-endo cyclization, and neophyl rearrangement. The exo/endo ratio is often dictated by concentration of reductant, where low concentrations favor formation of the 6-endo product. For more information, see: Chen, Z. M.; Zhang, X. M.; Tu, Y. Q. Radical Aryl Migration Reactions and Synthetic Applications. *Chem. Soc. Rev.* **2015**, *44* (15), 5220–5245



Scheme 2.1. Evidence of radical intermediate by radical cyclization

2.4 Conclusions

In conclusion, we have designed a simple catalytic system that enables the general, regioselective coupling of pyridine and diazine units to electron-poor alkenes. This method utilizes simple alkenes, stable aryl radical precursors (many of the shown substrates are commercially available), and a commercial catalyst. We describe how limiting the effective concentration of Hantzsch ester enables the employment of these reactive species in the formation of carbon–carbon bonds for the preparation of a diverse array of heterocycle-containing products. Studies to further elucidate the operational mechanistic details of this process, as well as the development of related transformations are ongoing in our laboratory. Acknowledgements Financial support was provided by Emory University and Winship Cancer Institute. We gratefully acknowledge Prof. Huw Davies for generous access to instrumentation and chemicals.

2.5 Experimental Information

2.5.1. General Reagent Information:

All reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (LEDwholesalers PAR38 Indoor Outdoor 16–Watt LED Flood Light Bulb, Blue; or PARsource PowerPAR LED Bulb-Blue 15 Watt/440 nm, available at www.eaglelight.com). Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photo redox catalyst, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$, was prepared according to a literature procedure.[45] Halogenated heteroarenes were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, Combi-Blocks, or Oakwood Products and were used as received, with the exception of Table 2.3, entries 9 and 14. Table 2.3, entries 9 and 14 were prepared according to the procedure in section IV, Preparation of Starting Materials. Ethyl crotonate and alkenes for Table 2.2, entries 1, 2, 3, and 6 were purchased from Alfa Aesar and Acros Organics and were used as received. Alkenes for Table 2.2, entries 9 and 10 were purchased from Combi-Blocks and were used as received. Furan-2(5H)-one used for Table 2, entry 13 was purchased from Alfa Aesar and was used as received. Alkenes for Table 2.2, entries 4[46], 5[47], 7[48], 8[49], 11[50], 12[51] were prepared according to literature procedures. Alkenes for Table 2.2, entries 14

[45] Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-Electron Transmetalation in Organoboron Cross-Coupling by Photoredox/Nickel Dual Catalysis. *Science (80-.).* **2014**, *345* (6195), 433–436.
[46] Mani, N. S.; Mapes, C. M.; Wu, J.; Deng, X.; Jones, T. K. Stereoselective Synthesis of Z-α-Aryl-α,β-Unsaturated Esters. *J. Org. Chem.* **2006**, *71* (13), 5039–5042.
[47] Brenna, E.; Gatti, F. G.; Manfredi, A.; Monti, D.; Parmeggiani, F. Enoate Reductase-Mediated Preparation of Methyl (S)-2-Bromobutanoate, a Useful Key Intermediate for the Synthesis of Chiral Active Pharmaceutical Ingredients. *Org. Process Res. Dev.* **2012**, *16* (2), 262–268.
[48] Eriksson, J.; Åberg, O.; Långström, B. Synthesis of [11C]/[13C]Acrylamides by Palladium-Mediated Carbonylation. *European J. Org. Chem.* **2007**, No. 3, 455–461.
[49] Evans, D. A.; Song, H. J.; Fandrick, K. R. Enantioselective Nitrone Cycloadditions of α,β-Unsaturated 2-Acyl Imidazoles Catalyzed by Bis(Oxazolinyl)Pyridine-Cerium(IV) Triflate Complexes. *Org. Lett.* **2006**, *8* (15), 3351–3354.
[50] Kohmoto, S.; Kobayashi, T.; Minami, J.; Ying, X.; Yamaguchi, K.; Karatsu, T.; Kitamura, A.; Kishikawa, K.; Yamamoto, M. Trapping of 1,8-Biradical Intermediates by Molecular Oxygen in Photocycloaddition of Naphthyl-N-(Naphthylcarbonyl)Carboxamides; Formation of Novel 1,8-Epidioxides and Evidence of Stepwise Aromatic Cycloaddition. *J. Org. Chem.* **2001**, *66* (1), 66–73.
[51] Stevens, C. V.; Van Heecke, G.; Barbero, C.; Patora, K.; De Kimpe, N.; Verhé, R. Synthesis of Substituted Cyclopropylphosphonates by Michael Induced Ring Closure (MIRC) Reactions. *Synlett* **2002**, No. 7, 1089–1092.

and 15 were prepared according to the designated procedures in section IV, Preparation of Starting Materials. DMSO was purified on a Pure Process Technologies solvent purification system. Reaction solvent was prepared by combining DMSO and tap water (3:1, v:v) which was degassed in a sidearm flask under weak vacuum while subject to sonication.

2.5.2 General Analytical Information:

All yields refer to isolated yields with the exception of Table 2, entry 6, which was determined by NMR with 1,2,3-trimethoxybenzene as an internal standard on a Mercury 300 MHz spectrometer. New compounds were characterized by NMR, IR spectroscopy, HRMS, and melting point. NMR data were recorded on one of five spectrometers: INOVA 600 MHz, INOVA 500 MHz, VNMR 400 MHz, INOVA 400 MHz, or Mercury 300 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; or Benzene-d_6: δ 7.15 for 1H NMR and 128.4 ppm for ^{13}C NMR). 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. Melting point data was obtained with a Thomas Hoover Unimelt capillary melting point apparatus. Optimization data was obtained via gas chromatography with an Agilent Technologies 7890B Gas Chromatography system (flame-ionization detection) equipped with an Agilent Technologies 19091J-413 HP-5 column (30 m x 0.320 mm x 0.25 µm, 5 % phenyl methyl siloxane) and an Agilent Technologies G4513A autoinjector.

2.5.3 General Procedures for Coupling of Halogenated Heteroarene with Alkene

General Procedure A:

A 30-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (1.3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (1 mol %), alkene (3 or 5 equiv), and halogenated heteroarene (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 (3:1 DMSO:H_2O, 10 mL/mmol heteroarene) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 18 hours or until consumption of the halogenated heteroarene was observed by gas chromatography. The reaction was quenched with saturated sodium bicarbonate solution (60 mL) and extracted with ethyl acetate (3 x 40 mL). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

General Procedure B:

A 30-mL screw-top test tube equipped with stir bar was charged with aryl halide (1 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ 1 mol %), sodium formate (3 equiv), 2,4,6-trimethylaniline (1 equiv), and alkene (3 equiv). The tube was sealed with a screw-cap 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 heteroarene) by syringe. The resulting

mixture was stirred under irradiation with blue LEDs overnight. The reaction was quenched with saturated sodium bicarbonate solution (60 mL) and extracted with ethyl acetate (3 x 40 mL). The extracts were combined, dried over magnesium sulfate, filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

Optimization Procedure B (Entry 5):

A 15-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (83 mg, 0.325 mmol, 1.3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.8 mg, 0.0025 mmol, 1 mol %), dimethyl 2-ethylidenemalonate (120 mg, 0.75 mmol, 3 equiv), and 2-iodopyridine (52 mg, 0.25 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 $(i\text{-pr})_2NEt$ (97 mg, 0.75mmol, 3 equiv) and degassed solvent (MeCN, 2.5 mL) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 18 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 acetone, and the solution was transferred to a 20-mL scintillation vial. An internal standard of dodecane (10 µL, 0.044 mmol) was delivered to the vial, and the contents were thoroughly mixed. A sample was analyzed by gas chromatography, and the integral values were used to calculate conversion, alkylpyridine (dimethyl 2-(1-(pyridin-2-yl)ethyl)malonate) yield, and hydrodehalogenation product (pyridine) yield.

Optimization Procedure C (Entries 6-22):

A 15-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (83 mg, 0.325 mmol, 1.3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.8 mg, 0.0025 mmol, 1 mol %), dimethyl 2-ethylidenemalonate (120 mg, 0.75 mmol, 3 equiv), and 2-iodopyridine (52 mg, 0.25 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 (MeCN, DMSO, 3:1 DMF:H_2O, 3:1 MeOH:H_2O, 3:1 MeCN:H_2O, or 3:1 DMSO:H_2O, 2.5 mL) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 18 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 acetone, and the solution was transferred to a 20-mL scintillation vial. An internal standard of dodecane (10 µL, 0.044 mmol) was delivered to the vial, and the contents were thoroughly mixed. A sample was analyzed by gas chromatography, and the integral values were used to calculate conversion, alkylpyridine (dimethyl 2-(1-(pyridin-2-yl)ethyl)malonate) yield, and hydrodehalogenation product (pyridine) yield.

Optimization Procedure D (Entry 22, air-exposed):

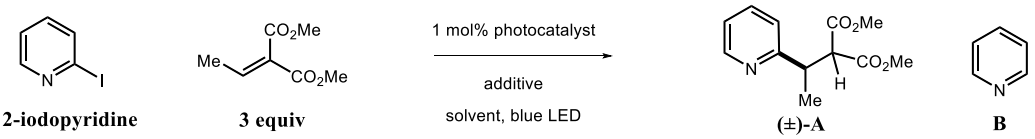
A 15-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (83 mg, 0.325 mmol, 1.3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.8 mg, 0.0025 mmol, 1 mol %), dimethyl 2-ethylidenemalonate (120 mg, 0.75 mmol, 3 equiv), and 2-iodopyridine (52 mg, 0.25 mmol, 1 equiv). The tube was charged with solvent (3:1 DMSO:H_2O, 2.5 mL) by syringe, and the tube was

sealed with PTFE/silicon septum. An 18 G needle pierced the septum for the duration of the reaction to allow for constant air exposure. The suspension was stirred under irradiation with blue LEDs for 18 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 acetone, and the solution was transferred to a 20-mL scintillation vial. An internal standard of dodecane (10 µL, 0.044 mmol) was delivered to the vial, and the contents were thoroughly mixed. A sample was analyzed by gas chromatography, and the integral values were used to calculate conversion, alkylpyridine (dimethyl 2-(1-(pyridin-2-yl)ethyl)malonate) yield, and hydrodehalogenation product (pyridine) yield.

2.5.4 Gas Chromatography Method Conditions:

The gas chromatography system hardware are reported in section I-B, General Analytical Information. The injection volume for each trial is 0.5 µL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. With no hold time, the temperature ramp rate is adjusted to 25 °C/min until reaching the maximum temperature of 325 °C. Maximum temperature is held for one minute before concluding the run.

Table S2.1: Heteroaryl RCA Optimization Table

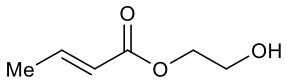


2-iodopyridine **3 equiv** **(±)-A** **B**

entry	photocatalyst	solvent	additive	% yield **A**	% yield **B**	selectivity (**A:B**)
1	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN	NEt_3 (3 eq)	24	5	5:1
2	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN	NBu_3 (3 eq)	29	6	5:1
3	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN	ipr_2NEt (3 eq)	12	3	4:1
4	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN	NBu_3 (3 eq), HCO_2H (3 eq)	27	5	5:1
5	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN	ipr_2NEt (3 eq), HEH (1.5 eq)	43	20	2:1
6	$Ru(bpy)_3Cl_2$	MeCN	HEH (1.3 eq)	24	6	4:1
7	$Ir(ppy)_3$	MeCN	HEH (1.3 eq)	53	13	4:1
8	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN	HEH (1.3 eq)	50	11	9:2
9	$Ir(ppy)_2dtbpy•PF_6$	MeCN	HEH (1.3 eq)	62	15	4:1
10	$Ru(bpy)_3Cl_2$	DMSO	HEH (1.3 eq)	50	15	7:2
11	$Ir(ppy)_3$	DMSO	HEH (1.3 eq)	68	25	7:2
12	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMSO	HEH (1.3 eq)	50	15	7:2
13	$Ir(ppy)_2dtbpy•PF_6$	DMSO	HEH (1.3 eq)	59	25	5:2
14	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMF/H_2O (3:1)	HEH (1.3 eq)	75	15	5:1
15	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeOH/H_2O (3:1)	HEH (1.3 eq)	78	10	8:1
16	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	MeCN/H_2O (3:1)	HEH (1.3 eq)	81	14	6:1
17[a]	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMSO/H_2O (3:1)	HEH (1.3 eq)	72	8	9:1
18[b]	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMSO/H_2O (3:1)	HEH (1.3 eq)	89	6	15:1
19[c]	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMSO/H_2O (3:1)	HEH (1.3 eq)	0	0	-
20	none	DMSO/H_2O (3:1)	HEH (1.3 eq)	20	2	10:1
21	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMSO/H_2O (3:1)	HEH (1.3 eq)	96	4	48:2
22[d]	$Ir(dF(CF_3)ppy)_2dtbpy•PF_6$	DMSO/H_2O (3:1)	HEH (1.3 eq)	92	4	45:2

[a]1.5 equiv dimethyl ethylidenemalonate. [b]2.0 equiv dimethyl ethylidenemalonate. [c]No light. [d]Exposed to open atmosphere.

2.5.5 Preparation of Starting Materials:



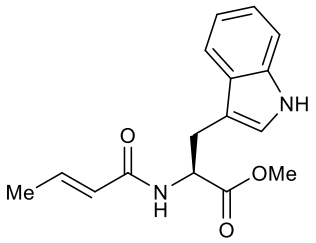
2-hydroxyethyl (E)-but-2-enoate: To a solution of pyridine (1.56 g, 15 mmol, 1.5 equiv) in ethylene glycol (50 mL) and THF (50 mL) at 0 °C was added but-2-enoyl chloride by syringe over 10 minutes. The mixture was allowed to warm to room temperature and continued stirring for 5.5 hours. The THF was removed by rotary evaporation, and the residual solution was partitioned between ethyl acetate (150 mL) and 1M HCl solution (100 mL). The layers were separated, and the organic phase was washed with 1M HCl solution (2 x 100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated by rotary evaporation to afford the title compound (1.10 g, 54% yield) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 – 6.66 (m, 1H), 5.68 (d, J = 15.7 Hz, 1H), 4.02 (t, J = 4.8 Hz, 2H), 3.70 (s, 1H), 3.61 (d, J = 4.8 Hz, 2H), 1.68 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3) δ 166.7, 145.3, 122.1, 65.6, 60.4, 17.8.

FTIR (neat) νmax: 3429, 2948, 2917, 2881, 2359, 1716, 1655, 1444, 1375, 1311, 1292, 1263, 1178, 1103, 1080, 1033, and 967 cm^{-1}.

HRMS (NSI) m/z: [M+Na]+ calcd. for $C6H_{10}O_3Na$, 153.0522; found, 153.0522.



Methyl (E)-but-2-enoyl-L-tryptophanate: To a solution of methyl L-tryptophanate (2.4 g, 9.4 mmol, 1 equiv) and pyridine (1.87 g, 23.6 mmol, 2.5 equiv) in dichloromethane (80 mL) at 0 °C was added but-2-enoyl chloride (1.01 g, 10.34 mmol, 1.1 equiv) by syringe over 10 minutes. The mixture was allowed to warm to room temperature and continued stirring for 3.5 hours. The solvent was removed by rotary evaporation, and the residue was dissolved in ethyl acetate (150 mL). The solution was washed with 1M HCl solution (3 x 100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation to afford the title compound (2.22 g, 82% yield) as a yellow solid.

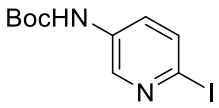
Mp: 118 – 120 °C

^{1}H NMR (300 MHz, CDCl3) δ 8.26 (s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.3, 6.7 Hz, 1H), 7.11 (td, J = 7.5, 2.9 Hz, 1H), 6.97 (d, J = 2.5 Hz, 1H), 6.85 (dq, J = 15.4, 6.5, 6.5 Hz, 1H), 6.01 (d, J = 7.9 Hz, 1H), 5.81 – 5.70 (m, 1H), 5.03 (dt, J = 7.9, 5.2 Hz, 1H), 3.69 (d, J = 0.6 Hz, 3H), 3.35 (d, J = 5.3 Hz, 2H), 1.82 (dd, J = 6.9, 1.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 165.5, 140.9, 136.1, 127.6, 124.6, 122.9, 122.2, 119.6, 118.6, 111.3, 109.9, 53.0, 52.4, 27.7, 17.8.

FTIR (neat) νmax: 3410, 3310, 2358, 2339, 1736, 1669, 1625, 1537, 1458, 1438, 1430, 1210, 1174, 967, and 738 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for C16H19N2O3, 287.1390; found, 287.1386.



Tert-butyl (6-iodopyridin-3-yl)carbamate: To a solution of 6-iodopyridin-3-amine (616.1 mg, 2.80 mmol, 1 equiv) in tetrahydrofuran (10 mL) at 0 °C was added a solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 5.60 mL, 2 equiv). After stirring the reaction at 0 °C for 30 mins and then room temperature 15 mins, di-tert-butyl dicarbonate (642.1 mg, 2.94 mmol, 1.05 equiv) was added slowly. The resulting mixture was stirred overnight at room temperature. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, water and brine. After drying over magnesium sulfate, the solid was filtered off and the filtrated was concentrated by rotary evaporation. The crude reaction mixture was purified by flash chromatography (hexane:ethyl acetate = 4:1) to afford the product (841.8 mg, 94% yield) as a white solid.

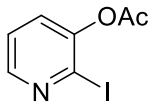
Mp: 136 – 138 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 2.8, 0.7 Hz, 1H), 7.68 (s, 1H), 7.59 (dd, J = 8.5, 0.6 Hz, 1H), 6.58 (s, 1H), 1.49 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 141.2, 135.9, 134.5, 127.9, 108.3, 81.4, 28.3.

FTIR (neat) ν_{max}: 3212, 3149, 2977, 1717, 1589, 1519, 1453, 1362, 1249, and 1150 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{14}N_2O_2I$, 263.9516; found, 263.9515.



2-iodopyridin-3-yl acetate: To a solution of 2-iodopyridin-3-ol (1.00 g, 4.54 mmol, 1 equiv) in dichloromethane (10 mL) at 0 °C was added triethylamine (1.30 mL, 9.33 mmol, 2 equiv) and acetyl chloride (0.50 mL, 7.03 mmol, 1.5 equiv) subsequently. The reaction was warmed slowly to room temperature in the ice-water bath and stirred overnight. It was then quenched with saturated sodium bicarbonate solution and extracted with dichloromethane three times. The combined organic layers were washed with saturated sodium bicarbonate solution, water and brine. After drying over magnesium sulfate, the solid was filtered off and the filtrate was concentrated by rotary evaporation. The crude reaction mixture was purified by flash column chromatography (hexane:ethyl acetate = 4:1) to afford the product (1.10 g, 92% yield) as a white solid.

Mp: 44 – 46 °C

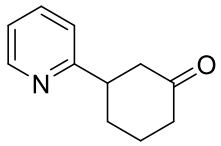
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 4.6, 1.7 Hz, 1H), 7.35 (dd, J = 8.0, 1.7 Hz, 1H), 7.30 – 7.06 (m, 1H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 148.6, 147.9, 130.1, 123.6, 115.5, 21.3.

FTIR (neat) ν_{max}: 3052, 1766, 1563, 1441, 1400, 1367, and 1173 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_7H_7NO_2I$, 263.9516; found, 263.9515.

2.5.6. Procedure and Characterization Data



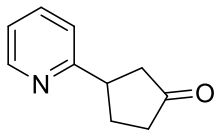
3-(pyridine-2-yl)cyclohexan-1-one (Table 2.2, entry 1): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), cyclohex-2-en-1-one (0.290 mL, 3.00 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (12.0 mg, 0.011 mmol, 0.011 equiv) and Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv) provided the product (148 mg, 85% yield) as a pale yellow oil after purification by flash column chromatography (hexanes:ethyl acetate = 3:1 then 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 4.6 Hz, 1H), 7.49 (td, J = 7.7, 1.9 Hz, 1H), 7.00 (dd, J = 7.6, 5.0 Hz, 2H), 3.17 – 2.90 (m, 1H), 2.68 (dd, J = 14.2, 11.9 Hz, 1H), 2.52 – 2.37 (m, 1H), 2.35 – 2.20 (m, 2H), 2.06 – 1.90 (m, 2H), 1.90 – 1.49 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 162.6, 149.2, 136.6, 121.7, 121.6, 46.7, 46.2, 41.1, 31.5, 25.1.

FTIR (neat) ν_{max}: 3007, 2937, 2862, 1706, 1588, 1434, 1221, 774, and 748 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{14}NO$, 176.1070; found, 176.1069.



3-(pyridine-2-yl)cyclopentan-1-one (Table 2.2, entry 2): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), cyclopent-2-en-1-one (0.251 mL, 3.00

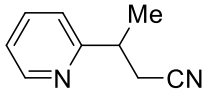
mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv) provided the product (134 mg, 84% yield) as a pale yellow oil after purification by flash column chromatography (hexanes:ethyl acetate = 3:1 then 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dd, J = 4.9, 0.9 Hz, 1H), 7.53 (td, *J* = 7.7, 1.9 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.08 – 6.97 (m, 1H), 3.46 (tdd, *J* = 9.5, 7.9, 6.1 Hz, 1H), 2.68 – 2.45 (m, 2H), 2.44 – 1.94 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 162.1, 149.4, 136.5, 122.0, 121.7, 44.4, 43.9, 38.3, 30.2.

FTIR (neat) ν_{max}: 3008, 2961, 2900, 1735, 1590, 1473, 1436, 1150, 1134, 785, and 749 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{12}NO$, 162.0913; found, 162.0912.



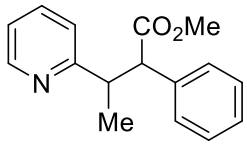
3-pyridin-2-yl(butanenitrile (Table 2.2, entry 3): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), crotononitrile (0.245 mL, 3.00 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.0 mg, 0.010 mmol, 0.010 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the product (101 mg, 72% yield) as a pale yellow oil after purification by flash column chromatography (hexanes:ethyl acetate = 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.24 – 7.06 (m, 2H), 3.34 – 3.18 (m, 1H), 2.80 (dd, *J* = 16.7, 6.7 Hz, 1H), 2.69 (dd, *J* = 16.6, 7.4 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 149.5, 136.8, 122.2, 121.8, 119.0, 38.3, 23.9, 20.1.

FTIR (neat) ν_{max}: 3053, 3010, 2971, 2931, 2875, 2246, 1590, 1570, 1474, 1435, 991, 785, and 749 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_9H_{11}N_2$, 147.0917; found, 147.0916.



Methyl 2-phenyl-3-(pyridin-2-yl)butanoate (Table 2.2, entry 4): following the general procedure, the reaction of 2-iodopyridine (125 mg, 0.61 mmol, 1 equiv), methyl 2-phenylbut-2-enoate (320 mg, 1.81 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (8.0 mg, 0.007 mmol, 0.012 equiv) and Hantzsch ester (179 mg, 0.71 mmol, 1.2 equiv) provided the product in an inseparable 4:3 mixture of diastereomers (128 mg, 84% yield) as colorless oil after purification by flash column chromatography (hexane:ethyl acetate = 20:1 then 10:1).

^{1}H NMR Major Diastereomers (300 MHz, Benzene-d_6) δ 8.34 (dt, J = 4.7, 1.4 Hz, 1H), 7.18 – 6.15 (m, ArH), 3.69 (ddd, J = 11.1, 6.8, 2.3 Hz, 2H), 3.24 (s, 3H), 1.54 (d, J = 6.7 Hz, 3H).

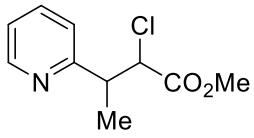
^{1}H NMR Minor Diastereomers, characteristic signals (300 MHz, Benzene-d_6) δ 8.45 (dt, J = 5.0, 1.3 Hz, 1H), 7.60 – 7.39 (m, 1H), 4.49 (d, J = 11.2 Hz, 1H), 3.00 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H).

For the mixture of diastereomers:

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 173.8, 164.2, 162.6, 149.2, 149.1, 137.7, 137.6, 136.4, 135.9, 128.7, 128.6, 128.3, 128.1, 127.5, 126.9, 123.2, 123.0, 121.4, 121.2, 57.4, 56.7, 52.0, 51.7, 45.7, 44.7, 19.8, 19.2.

FTIR (neat) ν_{max}: 3063, 3029, 3006, 2968, 2950, 2873, 2842, 1731, 1589, 1454, 1158, 733, and 698 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{18}NO_2$, 256.1334; found, 256.1332.



Methyl 2-chloro-3-(pyridine-2-yl)butanoate (Table 2.2, entry 5): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), methyl 2-chlorobut-2-enoate (420 mg, 3.12 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (331 mg, 1.31 mmol, 1.3 equiv) provided the product in an inseparable 4:1 mixture of diastereomers (185 mg, 87% yield) as a colorless oil after purification by flash column chromatography (hexane:ethyl acetate = 10:1 then 5:1).

^{1}H NMR Major Diastereomers (300 MHz, $CDCl_3$) δ 8.54 – 8.46 (m, 1H), 7.62 – 7.49 (m, 1H), 7.17 – 7.02 (m, 2H), 4.66 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.46-3.35 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H).

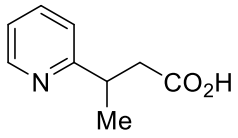
^{1}H NMR Minor Diastereomers, characteristic signals (300 MHz, $CDCl_3$) δ 8.44 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 4.77 (d, *J* = 8.2 Hz, 1H), 3.56 (s, 3H), 1.40 (d, *J* = 7.0 Hz, 3H).

For the mixture of diastereomers:

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 169.7, 161.1, 160.5, 149.4, 149.1, 136.6, 136.4, 123.4, 122.5, 122.1, 122.0, 61.6, 60.4, 52.8, 52.6, 46.0, 45.0, 18.0, 16.7.

FTIR (neat) ν_{max}: 2976, 2953, 2877, 1744 1593, 1570, 1435, 1273, 1194, 1162, 991, 786, and 748 cm^{-1}.

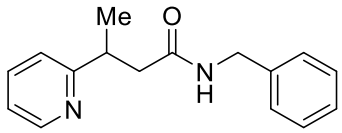
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{13}NO_2Cl$, 214.0629; found, 214.0629.



3-(pyridin-2-yl)butanoic acid (Table 2.2, entry 6):

A 30-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (83.0 mg, 0.33 mmol, 1.3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.8 mg, 0.010 mmol, 0.010 equiv), but-2-enoic acid (64.5 mg, 0.75 mmol, 3 equiv), and 2-iodopyridine (53 mg, 0.25 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 (3:1 DMSO:H_2O, 0.1 M) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 18 hours. The water was removed from the crude mixture by rotary evaporation. An internal standard of 1,3,5-trimethoxybenzene (43.8 mg, 0.26 mmol, 1.04 equiv) was added. Crude NMR of the mixture was taken (d1=10 s), and integration of the aromatic protons in the resultant ^1H spectrum indicated 74 % yield of the title compound.

^1H NMR, characteristic signals: (300 MHz, DMSO-d6) δ 8.81 (td, *J* = 5.9, 1.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.89 (ddd, *J* = 7.6, 5.8, 1.2 Hz, 1H), 3.59 – 3.43 (m, 1H), 2.90 (dd, *J* = 17.1, 8.6 Hz, 1H), 2.77 (dd, J = 17.1, 6.3 Hz, *1*H).



N-benzyl-3-(pyridine-2yl)butanamide (Table 2.2, entry 7): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), N-benzylbut-2-enamide (526 mg, 3.01mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.0 mg, 0.010 mmol, 0.010 equiv) and Hantzsch ester (331 mg, 1.31 mmol, 1.3 equiv) provided the product (171 mg, 70% yield) as a pale yellow oil after purification by flash column chromatography (hexanes:ethyl acetate = 1:1 then 1:2).

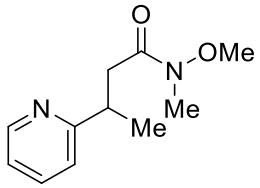
Mp: 70 – 72 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 – 8.33 (m, 1H), 7.53 (tdd, J = 7.6, 1.9, 0.9 Hz, 1H), 7.24 – 7.10 (m, 4H), 7.09 – 7.01 (m, 1H), 7.00 – 6.94 (m, 2H), 6.70 (s, 1H), 4.33 (dd, J = 14.9, 6.1 Hz, 1H), 4.19 (dd, J = 14.9, 5.4 Hz, 1H), 3.49 – 3.33 (m, 1H), 2.73 (dd, J = 13.9, 8.8 Hz, 1H), 2.49 (dd, J = 14.2, 6.0 Hz, 1H), 1.26 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, Chloroform-d) δ 171.87, 164.46, 148.90, 138.38, 136.66, 128.42, 127.38, 127.08, 122.71, 121.51, 43.19, 43.08, 38.64, 21.15.

FTIR (neat) ν_{max}: 3206, 3045, 2974, 2962, 2909, 1667, 1567, 1551, 1474, 1291, 1241, 792, 753, 736, and 705 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}N_2O$, 255.1492; found, 255.1491.



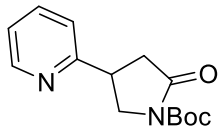
N-methoxy-N-methyl-3-(pyridin-2-yl)butanamide (Table 2.2, entry 8): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), N-methoxy-N-methylbut-2-enamide (387 mg, 3.00 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.4 mg, 0.010 mmol, 0.010 equiv) and Hantzsch ester (334 mg, 1.32 mmol, 1.3 equiv) provided the product (121 mg, 63% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 1:1 then ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (dt, J = 4.9, 0.9 Hz, 1H), 7.50 (td, J = 7.6, 1.9 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.01 (ddt, J = 7.5, 4.8, 1.0 Hz, 1H), 3.56 (s, 3H), 3.41 (dt, J = 14.1, 7.0 Hz, 1H), 3.04 (s, 3H), 2.97 (dd, J = 16.0, 7.6 Hz, 1H), 2.62 (dd, J = 16.1, 6.8 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 149.0, 136.4, 122.4, 121.2, 61.1, 38.2, 37.4, 21.0 (2xC).

FTIR (neat) ν_{max}: 3349, 2965, 2936, 2873, 1655, 1590, 1568, 1473, 1433, 1415, 1348, 1176, 1149, 1120, 997, 784, and 749 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}N_2O_2$, 209.1285; found, 209.1283.



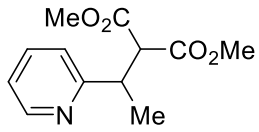
Tert-butyl 2-oxo-4-(pyridine-2-yl)pyrrolidine-1-carboxylate (Table 2.2, entry 9): following the general procedure, the reaction of 2-iodopyridine (205.0 mg, 1.00 mmol, 1 equiv), tert-butyl 2-oxo-4-pyridin-2-yl)pyrrolidine-1-carboxylate (560 mg, 3.06 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329.0 mg, 1.3 mmol, 1.3 equiv) provided the product (159 mg, 61% yield) as a colorless oil after purification by flash column chromatography (hexane:ethyl acetate = 5:1 then 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 – 8.48 (m, 1H), 7.65 – 7.53 (m, 1H), 7.13 (ddd, J = 7.6, 4.2, 1.0 Hz, 2H), 4.07 (dtd, J = 10.7, 8.6, 0.9 Hz, 1H), 3.84 (dt, J = 10.7, 8.6 Hz, 1H), 3.68 – 3.52 (m, 1H), 2.93 (dt, J = 17.4, 9.7 Hz, 1H), 2.76 (dt, J = 17.2, 8.7 Hz, 1H), 1.44 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.4, 149.8, 136.8, 122.4, 122.3, 82.8, 51.8, 39.1, 38.0, 28.0.

FTIR (neat) ν_{max}: 2978, 2931, 1779, 1746, 1711, 1367, 1350, 1300, 1285, 1255, 1147, 777, and 748 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{19}N_2O_3$, 263.1390; found, 263.1389.



Dimethyl 2-(1-pyridin-2-yl)ethyl)malonate (Table 2.2, entry 10): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), dimethyl 2-

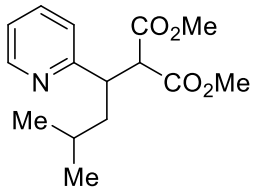
ethylidinemalonate (478 mg, 3.02 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.1 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (330 mg, 1.30 mmol, 1.3 equiv) provided the product (211 mg, 89% yield) as a pale yellow oil after purification by flash column chromatography (hexanes:diethyl ether = 5:3).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.50 (td, J = 7.6, 1.9 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.00 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 4.01 (d, J = 10.4 Hz, 1H), 3.66 (s, 3H), 3.60 – 3.51 (m, 1H), 3.42 (s, 3H), 1.20 (d, J = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 168.7, 149.0, 136.4, 122.8, 121.6, 56.5, 52.4, 52.1, 41.1, 19.1.

FTIR (neat) ν_{max}: 2954, 2846, 1751, 1731, 1434, 1287, 1271, 1252, 1218, 1192, 1146, 787, and 749 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{16}NO_4$, 238.1074; found, 238.1073.



Dimethyl 2-(2-methyl-1-(pyridin-2-yl)propyl)malonate (Table 2.2, entry 11): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), dimethyl 2-(3-methylbutylidene)malonate (606 mg, 3.03 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.0 mg, 0.010 mmol, 0.010 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the

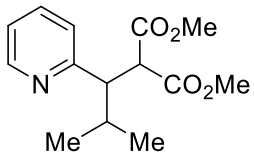
product (186 mg, 67% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 10:1 then 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 4.8 Hz, 1H), 7.60 – 7.47 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.10 – 7.01 (m, 1H), 3.96 (d, J = 10.5 Hz, 1H), 3.73 (s, 3H), 3.55 (td, J = 11.1, 3.2 Hz, 1H), 3.41 (s, 3H), 1.82 (td, J = 12.2, 3.2 Hz, 1H), 1.24 (ddd, J = 13.1, 10.1, 3.3 Hz, 1H), 1.17 -1.02 (m, 1H), 0.85 (d, J = 6.3 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.6, 160.8, 149.4, 135.9, 124.5, 121.6, 57.2, 52.5, 52.2, 44.8, 42.0, 25.1, 23.8, 21.0.

FTIR (neat) ν_{max}: 3007, 2954, 2869, 2947, 1753, 1734, 1570, 1434, 1258, 1243, 1145, 749, and 732 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{22}NO_4$, 280.1541; found, 280.1543.



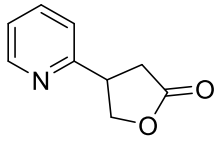
Dimethyl 2-(2-methyl-1-(pyridin-2-yl)propyl)malonate (Table 2.2, entry 12): following the general procedure, the reaction of 2-iodopyridine (164 mg, 0.80 mmol, 1 equiv), dimethyl 2-(2-methylpropylidene)malonate (446 mg, 2.40 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.0 mg, 0.010 mmol, 0.013 equiv) and Hantzsch ester (263 mg, 1.04 mmol, 1.3 equiv) provided the product (105 mg, 50% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 10:1 then 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 – 8.41 (m, 1H), 7.55 (td, *J* = 7.7, 1.9 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.5, 5.0 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 3.75 (s, 3H), 3.52 (d, *J* = 4.4 Hz, 1H), 3.45 (s, 3H), 2.06 – 1.86 (m, 1H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 168.9, 159.1, 148.5, 135.5 125.3, 121.5, 54.1, 52.6, 52.2, 51.6, 30.2, 21.5, 17.4.

FTIR (neat) ν_{max}: 2957, 2933, 2876, 2847, 1754, 1732, 1434, 1264, 1168, 1144, and 731 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{20}NO_4$, 266.1383; found, 266.1387.



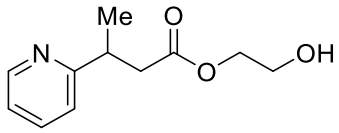
4-(pyridine-2-yl)dihydrofuran-2(3H)-one (Table 2.2, entry 13): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), furan-2(5H)-one (0.252 mg, 3.00 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.3 mmol, 1.3 equiv) provided the product (116 mg, 71% yield) as a yellow oil after purification by flash column chromatography (hexanes:ethyl acetate = 1:1 then 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.8 Hz, 1H), 7.59 (td, *J* = 7.7, 1.9 Hz, 1H), 7.14 (t, *J* = 6.5 Hz, 2H), 4.58 (t, *J* = 8.4 Hz, 1H), 4.36 (t, *J* = 8.3 Hz, 1H), 3.85 (p, *J* = 8.3 Hz, 1H), 2.91 (dd, *J* = 17.4, 8.6 Hz, 1H), 2.78 (dd, *J* = 17.4, 8.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 158.5, 149.8, 136.9, 122.6, 122.4, 72.8, 42.6, 34.3.

FTIR (neat) ν_{max}: 3054, 3009, 2911, 1770, 1592, 1160, 1019, 994, and 731 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_9H_{10}NO_2$, 164.0706; found, 164.0706.



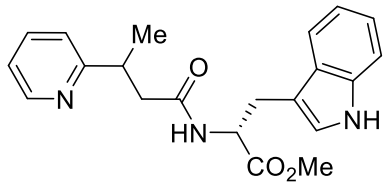
2-hydroxyethyl 3-(pyridin-2-yl)butanoate (Table 2.2, entry 14): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), 2-hydroxyethylbut-2-enoate (395 mg, 3.04 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.1 mg, 0.010 mmol, 0.010 equiv) and Hantzsch ester (333 mg, 1.32 mmol, 1.3 equiv) provided the product (142 mg, 68% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 1:1 then ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (dt, *J* = 4.9, 0.8 Hz, 1H), 7.56 (td, *J* = 7.7, 1.8 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.07 (td, *J* = 4.9, 4.9, 1.4 Hz, 1H), 4.15 (dt, *J* = 11.5, 4.6 Hz, 1H), 4.02 (dt, *J* = 11.5, 4.7 Hz, 1H), 3.66 (t, *J* = 4.7 Hz, 2H), 3.48 – 3.29 (m, 1H), 2.71 (dd, *J* = 15.3, 8.5 Hz, 1H), 2.58 (dd, *J* = 15.3, 6.3 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 164.0, 148.8, 136.9, 121.70, 121.65, 65.9, 60.3, 41.3, 38.1, 20.5.

FTIR (neat) ν_{max}: 3356, 2965, 2874, 1729, 1593, 1435, 1205, 1166, 786, and 750 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{16}NO_3$, 210.1125; found, 210.1124.



Methyl (3-(pyridin-2-yl)butanoyl)-D-tryptophanate (Table 2.2, entry 15): following the general procedure, the reaction of 2-iodopyridine (205 mg, 1.00 mmol, 1 equiv), methylbut-2-enoyl-D-tryptophanate (860 mg, 3.01 mmol, 3 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (11.0 mg, 0.010 mmol, 0.010 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the product in an inseparable 1:1 mixture of diastereomers (147 mg, 41% yield) as a yellow solid after purification by flash column chromatography (hexane:ethyl acetate = 1:1 then ethyl acetate).

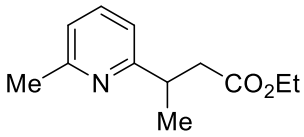
For the mixture of diastereomers:

^{1}H NMR (300 MHz, Benzene-d_6) δ 8.81 (s, $1H_{dr1}$+$1H_{dr2}$), 8.33 – 8.21 (m, $1H_{dr1}$+$1H_{dr2}$), 7.64 – 7.51 (m, $1H_{dr1}$+$1H_{dr2}$), 7.35 – 7.21 (m, $1H_{dr1}$+$1H_{dr2}$), 7.20 – 7.03 (m, $2H_{dr1}$+$2H_{dr2}$), 7.03 – 6.89 (m, $1H_{dr1}$+$1H_{dr2}$), 6.83 – 6.68 (m, $3H_{dr1}$+$3H_{dr2}$), 6.58 – 6.43 (m, $1H_{dr1}$+$1H_{dr2}$), 5.21 – 4.88 (m, $1H_{dr1}$+$1H_{dr2}$), 3.54 – 3.35 (m, $1H_{dr1}$+$1H_{dr2}$), 3.36 – 3.03 (m, $5H_{dr1}$+$5H_{dr2}$), 2.73 – 2.56 (m, $1H_{dr1}$+$1H_{dr2}$), 2.45 – 2.19 (m, $1H_{dr1}$+$1H_{dr2}$), 1.20 (d, J = 7.1 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, Benzene-d_6) δ 172.5, 172.4, 171.9, 164.7, 164.6, 148.73, 148.70, 136.7, 136.1, 127.9, 127.9, 123.3, 122.2, 122.1, 121.8, 121.2, 121.1, 119.3, 118.6, 111.6, 109.8, 109.7, 53.3, 53.2, 51.5, 42.4, 38.4, 27.7, 27.7, 20.8, 20.7.

FTIR (neat) ν_{max}: 3284, 3055, 3009, 2953, 2957, 2871, 1736, 1648, 1592, 1518, 1434, 1354, 1340, 1211, and 740 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{24}N_3O_3$, 366.1812; found, 366.1812.



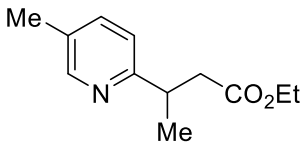
Ethyl 3-(6-methylpyridin-2-yl)butanoate (Table 2.3, entry 1): following the general procedure (A), the reaction of 2-bromo-6-methylpyridine (169.5 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.0 mg, 0.0053 mmol, 0.005 equiv) and Hantzsch ester (324.6 mg, 1.28 mmol, 1.3 equiv) provided the product (155.3 mg, 76% yield) as a pale yellow oil after purification by flash column chromatography (dichloromethane:diethyl ether = 50:1 then 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (t, J = 7.7 Hz, 1H), 6.94 (t, J = 7.6 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.41 – 3.30 (m, 1H), 2.82 (dd, J = 15.5, 7.2 Hz, 1H), 2.54 (dd, J = 15.5, 7.6 Hz, 1H), 2.49 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 163.5, 157.4, 136.3, 120.6, 118.0, 60.0, 40.8, 37.9, 24.3, 20.5, 14.0.

FTIR (neat): 2976, 1731, 1591, 1576, 1463, 1370, 1347, 1284, 1200, 1162 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{18}NO_2$, 208.1332; found, 208.1331.



Ethyl 3-(5-methylpyridin-2-yl)butanoate (Table 2.3, entry 2): following the general procedure (A), the reaction of 2-bromo-5-methylpyridine (172.3 mg, 1.00 mmol, 1 equiv), ethyl crotonate

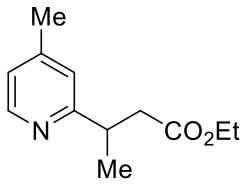
(0.62 mL, 4.99 mmol, 5 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5.7 mg, 0.0051 mmol, 0.005 equiv) and Hantzsch ester (310.3 mg, 1.26 mmol, 1.2 equiv) provided the product (127.9 mg, 62% yield) as a pale yellow oil after purification by flash column chromatography (hexane:diethyl ether = 4:1 then 2:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.38 (dd, J = 8.2, 1.9 Hz, 1H), 7.05 (d, J = 7.9 Hz, 1H), 4.08 – 4.01 (m, 2H), 3.39 – 3.31 (m, 1H), 2.82 (dd, J = 15.6, 7.6 Hz, 1H), 2.55 (dd, J = 15.6, 7.2 Hz, 1H), 2.27 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 161.2, 149.3, 136.8, 130.4, 121.1, 59.9, 40.8, 37.4, 20.6, 17.8, 13.9.

FTIR (neat): 2974, 1731, 1602, 1570, 1488, 1369, 1160 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{18}NO_2$, 208.1332; found, 208.1332.



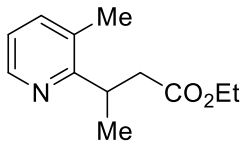
Ethyl 3-(4-methylpyridin-2-yl)butanoate (Table 2.3, entry 3): following the general procedure (A), the reaction of 2-bromo-4-methylpyridine (171.1 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (22.0 mg, 0.020 mmol, 0.02 equiv) and Hantzsch ester (318.8 mg, 1.26 mmol, 1.3 equiv) provided the product (169.0 mg, 82% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 9:1 then 8:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, J = 5.0 Hz, 1H), 6.97 (s, 1H), 6.90 (d, J = 5.0 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.36 – 3.29 (m, 1H), 2.82 (dd, J = 15.6, 7.6 Hz, 1H), 2.54 (dd, J = 15.6, 7.2 Hz, 1H), 2.29 (s, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 163.9, 148.6, 147.1, 122.5, 122.1, 59.8, 40.6, 37.7, 20.7, 20.5, 13.9.

FTIR (neat): 2975, 1731, 1605, 1561, 1460, 1369, 1177, 1158 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{18}NO_2$, 208.1332; found, 208.1331.



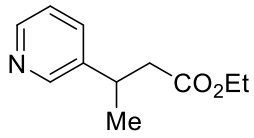
Ethyl 3-(3-methylpyridin-2-yl)butanoate (Table 2.3, entry 4): following the general procedure (A), the reaction of 2-iodo-3-methylpyridine (215.6 mg, 0.98 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.7 mg, 0.0051 mmol, 0.005 equiv) and Hantzsch ester (321.6 mg, 1.28 mmol, 1.3 equiv) provided the product (107.5 mg, 53% yield) as a pale yellow oil after purification by flash column chromatography (dichloromethane:diethyl ether = 50:1 then 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, J = 4.7 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 6.98 (dd, J = 7.6, 4.8 Hz, 1H), 4.06 – 3.96 (m, 2H), 3.63 – 3.55 (m, 1H), 2.96 (dd, J = 16.1, 8.3 Hz, 1H), 2.60 (dd, J = 16.1, 6.4 Hz, 1H), 2.36 (s, 3H), 1.22 (d, J = 6.9 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 162.5, 146.6, 137.6, 130.3, 121.0, 60.0, 40.1, 33.1, 20.1, 18.5, 14.0.

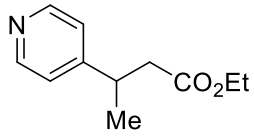
FTIR (neat): 2977, 1731, 1586, 1574, 1450, 1369, 1181, 1161 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{18}NO_2$, 208.1332; found, 208.1331.



Ethyl 3-(pyridin-3-yl)butanoate (Table 2.3, entry 5): following the general procedure (A), the reaction of 3-iodopyridine (194.9 mg, 0.95 mmol, 1 equiv), ethyl crotonate (0.31 mL, 2.49 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.9 mg, 0.0051 mmol, 0.006 equiv) and Hantzsch ester (317.2 mg, 1.25 mmol, 1.3 equiv) provided the product (95.7 mg, 52% yield) as a pale yellow solid after purification by flash column chromatography (hexane:diethyl ether = 9:1 then 1:1). The physical property and spectrum data match the reported value.[52]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, J = 2.0 Hz, 1H), 8.44 – 8.42 (m, 1H), 7.52 (dt, J = 7.9, 1.9 Hz, 1H), 7.20 (dd, J = 7.8, 4.8 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.32 – 3.24 (m, 1H), 2.58 – 2.55 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H).



Ethyl 3-(pyridin-4-yl)butanoate (Table 2.3, entry 6): following the general procedure (A), the reaction of 4-iodopyridine (203.3 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol,

[52] Sainsbury, M.; Weerasinghe, D.; Dolman, D. *J. Chem Soc., Perkin Trans. 1*. **1982**, 587-590.

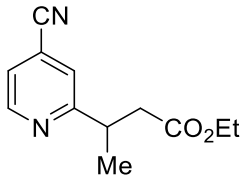
5 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5.8 mg, 0.0052 mmol, 0.005 equiv) and Hantzsch ester (313.1 mg, 1.24 mmol, 1.2 equiv) provided the product (92.3 mg, 48% yield) as a pale yellow oil after purification by flash column chromatography (dichloromethane:diethyl ether = 50:1 then 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, J = 5.5 Hz, 2H), 7.12 (d, J = 6.0 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.30 – 3.19 (m, 1H), 2.59 (dd, J = 15.5, 7.5 Hz, 1H), 2.53 (dd, J = 15.4, 7.6 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 154.5, 149.7, 122.1, 60.4, 41.7, 35.7, 21.0, 14.0.

FTIR (neat): 2976, 1731, 1599, 1559, 1457, 1415, 1371, 1284, 1173 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{12}NO_2$, 194.1176; found, 196.1174.



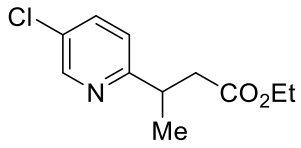
Ethyl 3-(4-cyanopyridin-2-yl)butanoate (Table 2.3, entry 7): following the general procedure (B), the reaction of 4-cyano-2-iodopyridine (228.6 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.37 mL, 2.98 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.3 mg, 0.010 mmol, 0.01 equiv), 2,4,6-trimethylaniline (0.14 mL, 1.0 mmol, 1 equiv) and sodium formate (208.6 mg, 3.07 mmol, 3.1 equiv) provided the product (112.5 mg, 52% yield) as a yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 9:1 then 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 5.0, 0.9 Hz, 1H), 7.42 – 7.41 (m, 1H), 7.33 (dd, J = 5.0, 1.5 Hz, 1H), 4.08 – 3.99 (m, 2H), 3.49 – 3.39 (m, 1H), 2.88 (dd, J = 16.1, 8.3 Hz, 1H), 2.59 (dd, J = 16.1, 6.3 Hz, 1H), 1.31 (d, J = 7.0 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 166.1, 150.0, 123.7, 122.7, 120.5, 116.5, 60.2, 40.1, 37.9, 20.5, 14.0.

FTIR (neat): 2978, 2238, 1729, 1595, 1551, 1474, 1398, 1370, 1279, 1179 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{15}N_2O_2$, 219.1128; found, 219.1127.



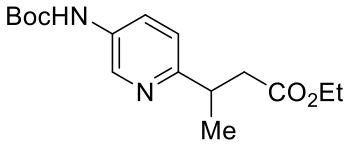
Ethyl 3-(5-chloropyridin-2-yl)butanoate (Table 2.3, entry 8): following the general procedure (A), the reaction of 5-chloro-2-iodopyridine (233.7 mg, 0.98 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.2 mg, 0.0055 mmol, 0.006 equiv) and Hantzsch ester (314.2 mg, 1.24 mmol, 1.3 equiv) provided the product (129.4 mg, 58% yield) as a pale yellow oil after purification by flash column chromatography (dichloromethane:diethyl ether = 100:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, J = 2.5 Hz, 1H), 7.55 (dd, J = 8.3, 2.5 Hz, 1H), 7.13 (d, J = 8.3 Hz, 1H), 4.08 – 4.01 (m, 2H), 3.42 – 3.33 (m, 1H), 2.82 (dd, J = 15.9, 8.0 Hz, 1H), 2.56 (dd, J = 15.9, 6.7 Hz, 1H), 1.28 (d, J = 8.2 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 157.9, 151.6, 149.6, 122.6, 121.0, 60.5, 41.5, 35.5, 20.9, 14.0.

FTIR (neat): 2976, 1731, 1579, 1560, 1471, 1369, 1349, 1275, 1161, 1112, 1013 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{15}Cl_1N_1O_3$, 228.0786; found, 228.0786.



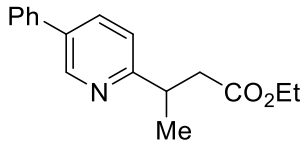
Ethyl 3-(5-((*tert*-butoxycarbonyl)amino)pyridin-2-yl)butanoate (Table 2.3, entry 9): following the general procedure (A), the reaction of *tert*-butyl (6-iodopyridin-3-yl)carbamate (320.2 mg, 1.00 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.3 mg, 0.0047 mmol, 0.005 equiv) and Hantzsch ester (315.5 mg, 1.25 mmol, 1.3 equiv) provided the product (148.9 mg, 48% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 4:1 then 1:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J = 2.5 Hz, 1H), 7.88 (s, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.49 (s, 1H), 4.08 – 4.01 (m, 2H), 3.41 – 3.29 (m, 1H), 2.79 (dd, J = 16.0, 8.0 Hz, 1H), 2.53 (dd, J = 15.6, 7.2 Hz, 1H), 1.49 (s, 9H), 1.27 (d, J = 7.8 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 158.4, 152.9, 139.6, 133.3, 126.4, 121.5, 80.7, 60.1, 40.9, 37.3, 28.1, 20.6, 14.0.

FTIR (neat): 3333, 2977, 1724, 1588, 1526, 1491, 1390, 1367, 1246, 1154 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{25}N_2O_4$, 309.1809; found, 309.1807.



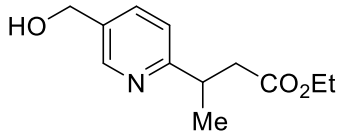
Ethyl 3-(5-phenylpyridin-2-yl)butanoate (Table 2.3, entry 10): following the general procedure (A), the reaction of 2-bromo-5-phenylpyridine (227.1 mg, 0.97 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.7 mg, 0.0051 mmol, 0.005 equiv) and Hantzsch ester (320.4 mg, 1.26 mmol, 1.3 equiv) provided the product (159.0 mg, 61% yield) as a pale yellow oil after purification by flash column chromatography (hexane:diethyl ether = 4:1 then 2:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, J = 2.4 Hz, 1H), 7.78 (ddd, J = 8.0, 2.4, 0.7 Hz, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.4 Hz, 1H), 7.26 – 7.23 (m, 1H), 4.10 – 4.04 (m, 2H), 3.49 – 3.42 (m, 1H), 2.90 (dd, J = 15.7, 7.7 Hz, 1H), 2.61 (dd, J = 15.7, 7.1 Hz, 1H), 1.35 (d, J = 7.0 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 163.2, 147.5, 137.8, 134.8, 134.3, 128.9, 127.7, 126.9, 121.7, 60.2, 40.8, 37.7, 20.7, 14.1.

FTIR (neat): 2975, 1731, 1596, 1558, 1476, 1449, 1369, 1278, 1161 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{20}NO_2$, 270.1489; found, 270.1487.



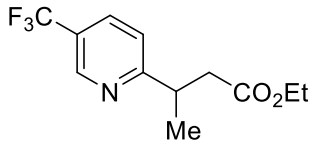
Ethyl 3-(5-(hydroxymethyl)pyridin-2-yl)butanoate (Table 2.3, entry 11): following the general procedure (A), the reaction of (6-bromo-pyridin-3-yl)methanol (190.0 mg, 1.01 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $Ir(dtbbpy)(ppy)_2]PF_6$ (4.6 mg, 0.0050 mmol, 0.005 equiv) and Hantzsch ester (333.9 mg, 1.32 mmol, 1.3 equiv) provided the product (167.9 mg, 74% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 1:1 then 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 1.9 Hz, 1H), 7.62 (dd, J = 8.0, 2.3 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 4.66 (s, 2H), 4.10 – 3.98 (m, 2H), 3.46 – 3.34 (m, 1H), 2.84 (dd, J = 15.7, 7.7 Hz, 1H), 2.57 (dd, J = 15.7, 7.0 Hz, 1H), 1.77 (br.s, 1H), 1.29 (d, J = 7.0 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 163.1, 147.5, 135.7, 134.4, 121.5, 61.7, 60.2, 40.7, 37.6, 20.5, 13.9.

FTIR (neat): 3366 (br.), 2976, 1729, 1602, 1571, 1489, 1458, 1370, 1278, 1163 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{18}NO_3$, 224.1281; found, 224.1281.



Ethyl 3-(5-(trifluoromethyl)pyridin-2-yl)butanoate (Table 2.3, entry 12): following the general procedure (A), the reaction of 2-iodo-5-trifluoromethylpyridine (271.3 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.7 mg, 0.0051 mmol, 0.005 equiv) and Hantzsch ester (306.8 mg, 1.21 mmol, 1.2 equiv) provided the product (176.4 mg, 68% yield) as a pale yellow oil after purification by flash column chromatography (dichloromethane:diethyl ether = 100:1 then 50:1).

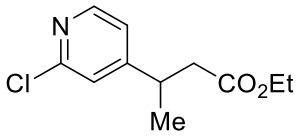
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (br.s, 1H), 7.81 (dd, J = 8.2, 2.4 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 4.08 – 4.01 (m, 2H), 3.51 – 3.40 (m, 1H), 2.90 (dd, J = 16.1, 8.2 Hz, 1H), 2.60 (dd, J = 16.0, 6.4 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 168.4, 146.0 (q, J = 4.1 Hz, δ = 146.06, 146.02, 145.99, 145.96), 133.3 (q, J = 3.5 Hz, δ = 133.35, 133.33, 133.30, 133.27), 124.3 (q, J = 3.3 Hz, δ = 126.82, 124.66, 122.50, 120.34), 123.6 (q, J = 270.4 Hz, δ = 124.66, 124.41, 124.15, 123.89), 121.8, 60.2, 40.3, 38.0, 20.5, 13.9.

^{19}F NMR ($CDCl_3$) δ -62.28.

FTIR (neat): 2979, 1734, 1607, 1574, 1460, 1400, 1371, 1328, 1160, 1130 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{15}NO_2F_3$, 262.1049; found, 262.1047.



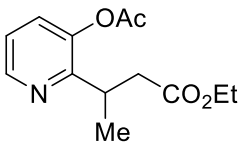
Ethyl 3-(2-chloropyridin-4-yl)butanoate (Table 2.3, entry 13): following the general procedure (A), the reaction of 2-chloro-4-iodopyridine (240.1 mg, 1.00 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (7.5 mg, 0.0067 mmol, 0.007 equiv) and Hantzsch ester (317.2 mg, 1.25 mmol, 1.3 equiv) provided the product (120.2 mg, 53% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 9:1 then 4:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 5.1 Hz, 1H), 7.17 (s, 1H), 7.06 (d, J = 5.1 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.30 – 3.19 (m, 1H), 2.60 – 2.51 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 157.9, 151.6, 149.6, 122.6, 121.0, 60.5, 41.4, 35.5, 20.9, 14.0.

FTIR (neat): 2976, 1729, 1592, 1545, 1466, 1392, 1370, 1278, 1203, 1131 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{15}Cl_1N_1O_3$, 228.0786; found, 228.0787.



Ethyl 3-(3-acetoxypyridin-2-yl)butanoate (Table 2.3, entry 14): following the general procedure (A), the reaction of 2-iodopyridin-3-yl acetate (260.6 mg, 0.99 mmol, 1 equiv), ethyl

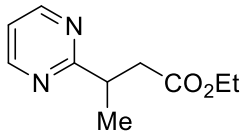
crotonate (0.62 mL, 4.99 mmol, 5 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5.6 mg, 0.0050 mmol, 0.005 equiv) and Hantzsch ester (330.2 mg, 1.30 mmol, 1.3 equiv) provided the product (145.8 mg, 58% yield) as a pale yellow oil after purification by flash column chromatography (hexane:diethyl ether = 4:1 then 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 4.7, 1.5 Hz, 1H), 7.36 (dd, J = 8.2, 1.5 Hz, 1H), 7.15 (dd, J = 8.1, 4.7 Hz, 1H), 4.10 – 3.98 (m, 2H), 3.63 – 3.53 (m, 1H), 2.85 (dd, J = 15.9, 7.6 Hz, 1H), 2.57 (dd, J = 15.9, 7.0 Hz, 1H), 2.35 (s, 3H), 1.23 (d, J = 6.9 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 168.9, 156.4, 146.5, 144.3, 130.0, 121.8, 60.1, 39.8, 31.1, 20.8, 19.6, 13.9.

FTIR (neat): 2979, 1768, 1730, 1593, 1545, 1441, 1370, 1290, 1192, 1156, 1091 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{18}NO_4$, 252.1230; found, 252.1229.



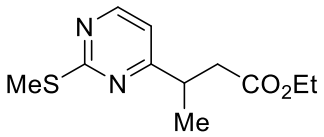
Ehyl 3-(pyrimidin-2-yl)butanoate (Table 2.3, entry 15): following the general procedure (B), the reaction of 2-bromopyrimidine (160.5 mg, 1.01 mmol, 1 equiv), ethyl crotonate (0.37 mL, 2.98 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.7 mg, 0.010 mmol, 0.01 equiv), 2,4,6-trimethylaniline (0.14 mL, 1.0 mmol, 1 equiv) and sodium formate (223.7 mg, 3.29 mmol, 3.3 equiv) provided the product (77.4 mg, 39% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 4:1 then 1:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (d, J = 4.9 Hz, 2H), 7.09 (t, J = 4.9 Hz, 1H), 4.08 – 4.02 (m, 2H), 3.60 – 3.51 (m, 1H), 2.98 (dd, J = 16.0, 8.3 Hz, 1H), 2.61 (dd, J = 16.0, 6.5 Hz, 1H), 1.35 (d, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125MHz, $CDCl_3$) δ 173.1, 172.3, 156.8, 118.5, 60.1, 39.7, 39.2, 20.0, 14.0.

FTIR (neat): 2976, 1731, 1571, 1561, 1463, 1424, 1369, 1282, 1258, 1177 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}N_2O_2$, 195.1128; found, 195.1128.



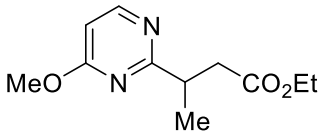
Ethyl 3-(2-(methylthio)pyrimidin-4-yl)butanoate (Table 2.3, entry 16): following the general procedure (A), the reaction of 4-iodo-2-(methylthio)pyrimidine (248.0 mg, 0.98 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.4 mg, 0.0057 mmol, 0.006 equiv) and Hantzsch ester (318.5 mg, 1.26 mmol, 1.3 equiv) provided the product (160.9 mg, 68% yield) as a pale yellow oil after purification by flash column chromatography (hexane:diethyl ether = 4:1 then 2:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, J = 5.1 Hz, 1H), 6.83 (d, J = 5.1 Hz, 1H), 4.09 – 4.03 (m, 2H), 3.33 – 3.25 (m, 1H), 2.88 (dd, J = 16.1, 7.9 Hz, 1H), 2.56 – 2.51 (m, 4H), 1.28 (d, J = 7.0 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.9, 171.8, 156.8, 114.3, 60.1, 39.3, 37.2, 19.8, 13.9, 13.7.

FTIR (neat): 2976, 1730, 1562, 1542, 1424, 1367, 1342, 1326, 1200, 1182, 1160 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}N_2O_2S$, 241.1005; found, 241.1005.



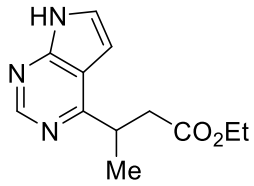
Ethyl 3-(4-methoxypyrimidin-2-yl)butanoate (Table 2.3, entry 17): following the general procedure (A), the reaction of 2-iodo-4-methoxypyrimidine (233.8 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $Ir(dtbbpy)(ppy)_2]PF_6$ (4.7 mg, 0.0051 mmol, 0.005 equiv) and Hantzsch ester (310.2 mg, 1.22 mmol, 1.2 equiv) provided the product (152.2 mg, 68% yield) as a pale yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 1:1 then 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 5.8 Hz, 1H), 6.51 (d, J = 5.8 Hz, 1H), 4.10 – 4.03 (m, 2H), 3.93 (s, 3H), 3.53 – 3.39 (m, 1H), 2.94 (dd, J = 15.9, 8.1 Hz, 1H), 2.56 (dd, J = 15.9, 6.7 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 172.4, 169.1, 156.8, 105.3, 59.9, 53.1, 39.5, 38.9, 19.7, 14.0.

FTIR (neat): 2979, 1732, 1568, 1473, 1418, 1367, 1327, 1312, 1276, 1174 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{17}N2O_3$, 225.1234; found, 225.1235.



Ethyl 3-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)butanoate (Table 2.3, entry 18): following the general procedure (A), the reaction of 4-iodo-7-h-pyrrolo[2,3-d]pyrimidine (119.6 mg, 0.49 mmol, 1 equiv), ethyl crotonate (0.31 mL, 2.49 mmol, 5 equiv), $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (3.1 mg, 0.0051 mmol, 0.006 equiv) and Hantzsch ester (156.2 mg, 0.62 mmol, 1.3 equiv) provided the product (86.5 mg, 76% yield) as a pale yellow solid after purification by flash column chromatography (hexane:diethyl ether = 4:1 then 2:1).

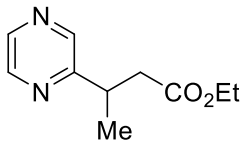
M.P. : 62-64 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.25 (br.s, 1H), 8.81 (s, 1H), 7.31 (dd, J = 3.4, 2.3 Hz, 1H), 6.66 (dd, J = 3.3, 1.7 Hz, 1H), 4.07 – 3.98 (m, 2H), 3.87 – 3.79 (m, 1H), 3.04 (dd, J = 16.1, 7.9 Hz, 1H), 2.71 (dd, J = 16.1, 6.8 Hz, 1H), 1.40 (d, J = 7.0 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 165.4, 151.5, 150.7, 125.2, 116.7, 99.5, 60.3, 39.6, 35.2, 20.0, 14.0.

FTIR (neat): 3200 (br.), 3133 (br.), 2978, 1731, 1582, 1505, 1465, 1418, 1350, 1286, 1254, 1184 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{12}H_{16}N_3O_2$, 234.1237; found, 234.1236.



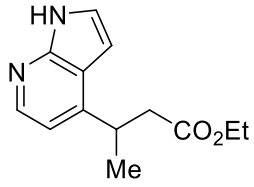
Ethyl 3-(pyrazin-2-yl)butanoate (Table 2.3, entry 19): following the general procedure (B), the reaction of 2-iodopyrazine (207.0 mg, 1.00 mmol, 1 equiv), ethyl crotonate (0.37 mL, 2.98 mmol, 3 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (11.1 mg, 0.010 mmol, 0.01 equiv), 2,4,6-trimethylaniline (0.14 mL, 1.0 mmol, 1 equiv) and sodium formate (204.8 mg, 3.01 mmol, 3.0 equiv) provided the product (102.1 mg, 52% yield) as a yellow oil after purification by flash column chromatography (hexane:ethyl acetate = 8:2 then 7:3).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, J = 1.4 Hz, 1H), 8.47 – 8.45 (m, 1H), 8.38 (d, J = 2.5 Hz, 1H), 4.11 – 3.96 (m, 2H), 3.53 – 3.39 (m, 1H), 2.85 (dd, J = 16.0, 8.2 Hz, 1H), 2.60 (dd, J = 16.0, 6.5 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 159.7, 143.9, 143.8, 142.4, 60.2, 40.1, 35.3, 20.4, 13.9.

FTIR (neat): 2977, 1731, 1526, 1473, 1407, 1371, 1346, 1279, 1179, 1140, 1033 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{15}N_2O_2$, 195.1128; found, 195.1126.



Ethyl 3-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)butanoate (Table 2.3, entry 20): following the general procedure (A), the reaction of 4-bromo-7-azaindole (195.4 mg, 0.99 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5.9 mg, 0.0053 mmol,

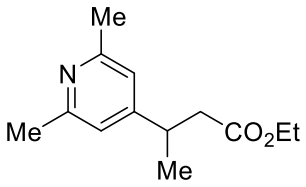
0.005 equiv) and Hantzsch ester (317.6 mg, 1.25 mmol, 1.3 equiv) provided the product (122.5 mg, 53% yield) as a pale yellow oil after purification by flash column chromatography (hexane:diethyl ether = 1:3 then diethyl ether).

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.45 (br.s, 1H), 8.24 (d, J = 5.0 Hz, 1H), 7.32 (dd, J = 3.6, 1.5 Hz, 1H), 6.93 (d, J = 5.0 Hz, 1H), 6.58 (d, J = 3.3 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.75 – 3.68 (m, 1H), 2.79 (dd, J = 15.3, 6.6 Hz, 1H), 2.66 (dd, J = 15.3, 8.4 Hz, 1H), 1.41 (d, J = 7.0 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 148.9, 147.4, 142.6, 124.7, 119.1, 112.6, 98.9, 60.4, 41.5, 33.8, 20.5, 14.1.

FTIR (neat): 3143 (br.), 2976, 1730, 1589, 1501, 1445, 1408, 1370, 1273, 1177 cm-1.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{17}NO_2$, 233.1285; found, 233.1286.



Ethyl 3-(2,6-dimethylpyridin-4-yl)butanoate (Table 2.3, entry 21): following the general procedure (A), the reaction of 4-bromo-2,6-dimethylpyridine (189.8 mg, 1.02 mmol, 1 equiv), ethyl crotonate (0.62 mL, 4.99 mmol, 5 equiv), $Ir(dtbbpy)(ppy)_2]PF_6$ (4.8 mg, 0.0053 mmol, 0.005 equiv) and Hantzsch ester (304.7 mg, 1.20 mmol, 1.2 equiv) provided the product (119.6 mg, 53% yield) as a pale yellow oil after purification by flash column chromatography (hexane:diethyl ether = 1:1 then 1:2).

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.79 (s, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.19 – 3.11 (m, 1H), 2.56 (dd, J = 15.4, 7.3 Hz, 1H), 2.52 – 2.43 (m, 7H), 1.24 (d, J = 7.0 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 157.5, 155.0, 116.1, 60.2, 41.7, 35.6, 24.2, 21.0, 14.0.

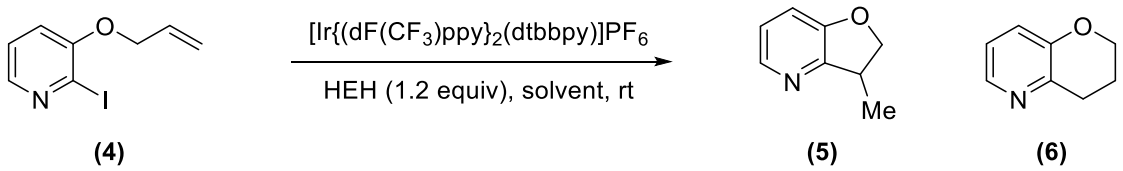
FTIR (neat): 2968, 1732, 1606, 1567, 1426, 1370, 1283, 1252, 1226, 1177, 1160 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{20}NO_2$, 222.1489; found, 222.1487.

2.5.6 Procedure for determination of Hantzsch ester solubility:

A 1,000 µL aliquot of DMSO or DMSO:H_2O (1:1, 2:1, 3:1, 4:1, 5:1, or 10:1) was delivered to a test tube. The solution was saturated with excess Hantzsch ester (200 mg, 0.79 mmol), and collidine (10 µL, 10.9 mg, 0.090 mmol) was added as an internal standard. The saturated solution was drawn into a syringe through a syringe filter. The syringe filter was removed, and the solution was delivered to a fresh test tube. The Hantzsch ester was oxidized to Hantzsch pyridine by sparging the solution with air for 2 hours. The sample was analyzed by gas chromatography, and integral values were used to calculate the mass of Hantzsch ester dissolved in solution.

2.5.7 Procedure for Intramolecular Cyclization:



(4) **(5)** **(6)**

Scheme S2.1: Radical Cyclization

Cyclization reactions suggesting radical mechanism:

Following the general procedure (A), the reaction of 3-(allyloxy)-2-iodopyridine[53] (compound **4**, 129.8 mg, 0.50 mmol, 1 equiv), [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5.1 mg, 0.0045 mmol, 0.01 equiv) and Hantzsch ester (153.3 mg, 0.61 mmol, 1.2 equiv) provided the known cyclization products 3-methyl-2,3-dihydrofuro[3,2-b]pyridine (**5**)[54] and 3,4-dihydro-2H-pyrano[3,2-b]pyridine (**6)**[55] (13% and 33% yield, respectively; yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard). The compounds were isolated by preparative TLC with (hexanes:ethyl acetate = 1:1). The spectra and physical properties match the reported data.

3-methyl-2,3-dihydrofuro[3,2-b]pyridine (5):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 1H), 7.02 – 6.95 (m, 2H), 4.76 (t, J = 9.1 Hz, 1H), 4.15 (dd, J = 8.8, 7.4 Hz, 1H), 3.59 – 3.48 (m, 1H), 1.39 (d, J = 7.0 Hz, 3H).

[53] Fantasia, S.; Windisch, J.; Scalone, M. *Adv. Synth. Catal.* **2013**, *355*, 627-631.
[54] Dahlen, A.; Petersson, A.; Hilmersson, G. *Org. Biomol. Chem.* **2003**, *1*, 2423-2426.
[55] Sliwa, H.; Blondeau, D.; Rydzkowski, R. *J. Heterocyclic Chem.* **1983**, *20*, 1613-161.

3,4-dihydro-2H-pyrano[3,2-b]pyridine (6):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 4.5, 1.3 Hz, 1H), 7.17 – 6.77 (m, 2H), 4.20 – 4.12 (m, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.12 – 2.06 (m, 2H).

Chapter 3

A practical and scalable system for heteroaryl amino acid synthesis

Adapted from: R. A. Aycock, D. B. Vogt, and N. T. Jui. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* **2017**, 8, 7998–8003.

D. B. Vogt contributed an improved synthesis of the chiral oxazolidinone radical acceptor, the scope of radical precursors that couple with it, and fluorescence quenching studies.

3.1 Abstract

A robust system for the preparation of β-heteroaryl α-amino acid derivatives has been developed using photoredox catalysis. This system operates *via* regiospecific activation of halogenated pyridines (or other heterocycles) and conjugate addition to dehydroalanine derivatives to deliver a wide range of unnatural amino acids. This process was conducted with good efficiency on large scale, the application of these conditions to amino ketone synthesis is shown, and a simple protocol is given for the preparation of enantioenriched amino acid synthesis, from a number of radical precursors.

3.2 Introduction

Amino acids play a central role in the chemical and biological sciences. As primary members of the chiral pool, they are precursors to drugs,[1] chiral auxiliaries,[2] and catalysts.[3] In addition, they are fundamental building blocks for the construction of biomolecules. The use of peptides as therapeutic agents is attractive because they can display extremely diverse, potent, and selective biological activities.[4] However, there are significant challenges in peptide drug design, including low metabolic stability or poor physical properties. One proven strategy for overcoming these challenges involves

[1] (a) Deacon, C. F. Dipeptidyl Peptidase-4 Inhibitors in the Treatment of Type 2 Diabetes: A Comparative Review. *Diabetes, Obes. Metab.* **2011**, *13* (1), 7–18. (b) Tsantrizos, Y. S. Peptidomimetic Therapeutic Agents Targeting the Protease Enzyme of the Human Immunodeficiency Virus and Hepatitis C Virus. *Acc. Chem. Res.* **2008**, *41* (10), 1252–1263.

[2] (a) Evans, D. A.; Helmchen, G; and Reuping, M. in *Asymmetric Synthesis: The Essentials*, **2007**, pp. 3-9. (b) Gnas, Y.; Glorius, F. Chiral Auxiliaries - Principles and Recent Applications. *Synthesis (Stuttg).* **2006**, No. 12, 1899–1930.

[3] (a) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, *107* (12), 5713–5743. (b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides. *Chem. Rev.* **2007**, *107* (12), 5759–5812. (c) Corey, E. J.; Helal, C. J. Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method. *Angew. Chemie Int. Ed.* **1998**, *37*, 1986–2012. (d) Helmchen, G.; Pfaltz, A. Phosphinooxazolines - A New Class of Versatile, Modular P,N-Ligands for Asymmetric Catalysis. *Acc. Chem. Res.* **2000**, *33* (6), 336–345. (e) Yang, A.; Ha, S.; Ahn, J.; Kim, R.; Kim, S.; Lee, Y.; Kim, J.; Söll, D.; Lee, H. Y.; Park, H. S. A Chemical Biology Route to Site-Specific Authentic Protein Modifications. *Science.* **2016**, *354* (6312), 623–626. (f) MacMillan, D. W. C. The Advent and Development of Organocatalysis. *Nature* **2008**, *455* (7211), 304–308. (g) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon-Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123* (22), 5260–5267. (h) Bertelsen, S.; Jørgensen, K. A. Organocatalysis - After the Gold Rush. *Chem. Soc. Rev.* **2009**, *38* (8), 2178–2189.

[4] (a) Kaspar, A. A.; Reichert, J. M. Future Directions for Peptide Therapeutics Development. *Drug Discov. Today* **2013**, *18* (17–18), 807–817. (b) Fosgerau, K.; Hoffmann, T. Peptide Therapeutics: Current Status and Future Directions. *Drug Discov. Today* **2015**, *20* (1), 122–128.

substitution of the native residues with unnatural amino acids (synthetic mutagenesis).[5] Nitrogen-containing heteroaromatics are common in pharmaceuticals because they directly alter the solubility,

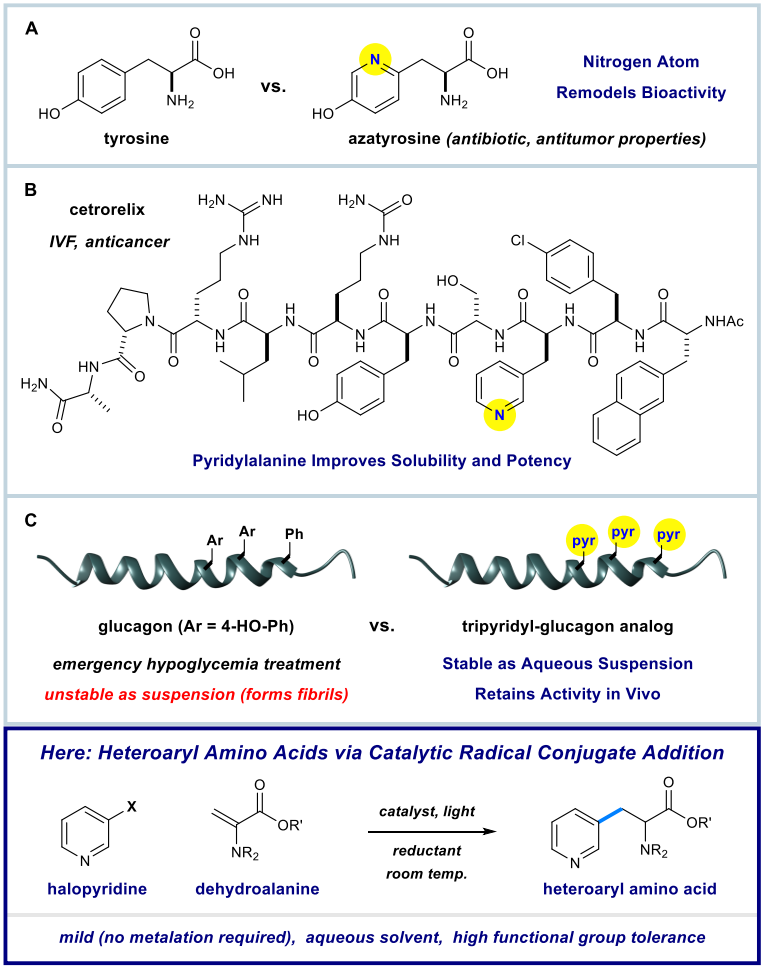


Figure 3.1. Impact of pyridine incorporation into amino acids and peptide drugs

[5] (a) Blaskovich, M. A. T. Unusual Amino Acids in Medicinal Chemistry. *J. Med. Chem.* **2016**, *59* (24), 10807–10836. (b) Reissmann, T.; Schally, A. V.; Bouchard, P.; Riethmüller, H.; Engel, J. The LHRH Antagonist Cetrorelix: A Review. *Hum. Reprod. Update* **2000**, *6* (4), 322–331. (c) Asami, T.; Nishizawa, N.; Matsui, H.; Nishibori, K.; Ishibashi, Y.; Horikoshi, Y.; Nakayama, M.; Matsumoto, S. I.; Tarui, N.; Yamaguchi, M.; Matsumoto, H.; Ohtaki, T.; Kitada, C. Design, Synthesis, and Biological Evaluation of Novel Investigational Nonapeptide KISS1R Agonists with Testosterone-Suppressive Activity. *J. Med. Chem.* **2013**, *56* (21), 8298–8307.

metabolic stability, and binding affinity of the molecules that they comprise.[6] As such, heteroarene-containing unnatural amino acids are promising tools in the design of peptide therapeutics. Pyridine incorporation has a dramatic impact on the properties of amino acids and peptides. For example, azatyrosine—a natural product that differs from the essential amino acid tyrosine by substitution of a single atom—displays potent antibiotic and antitumor properties (Figure 3.1A).[7] Installation of the 3-pyridylalanine (3-pyr-Ala) residue in the gonadotropin-releasing hormone antagonist cetrorelix (Figure 3.1B) was found to improve both aqueous solubility and receptor affinity,[8] and similar effects were observed in the development of other peptide hormones (Figure 3.1C).[5b,c] As part of a program centered on the catalytic functionalization of heteroaromatics, we target the development of impactful synthetic methods for the construction of novel β-heteroaryl α-amino acids through a radical conjugate addition mechanism. We have found that pyridyl halide activation *via* single electron reduction using photoredox catalysts[9] can be accomplished, and that the intermolecular reactivity of the resulting radical species can be dictated by the reaction conditions.[10,11] More specifically, we found that pyridyl radicals display nucleophilic reactivity in aqueous DMSO, and they readily couple with electron-poor alkenes. We

[6] (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. (b) Ritchie, T. J.; MacDonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. The Developability of Heteroaromatic and Heteroaliphatic Rings - Do Some Have a Better Pedigree as Potential Drug Molecules than Others? *Medchemcomm* **2012**, *3* (9), 1062–1069.

[7] (a)Myers, A. G.; Gleason Arnold, J. L.; Beckman, M. A Practical Synthesis of L-Azatyrosine. *Proc. Natl. Acad. Sci. U.S.A* **1991**, *11* (6), 813–815. (b) Doi, S.; Kimura, M.; Katsuki, M. Inhibition of Chemical Carcinogenesis in Vivo by Azatyrosine. *Cancer Res.* **1992**, *52* (6), 1628–1630.

[8] Beckers, T.; Bernd, M.; Kutscher, B.; Kühne, R.; Hoffmann, S.; Reissmann, T. Structure-Function Studies of Linear and Cyclized Peptide Antagonists of the GnRH Receptor. *Biochem. Biophys. Res. Commun.* **2001**, *289* (3), 653–663.

[9] (a) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116* (17), 10075–10166. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113* (7), 5322–5363

[10] Aycock, R. A.; Wang, H.; Jui, N. T. A Mild Catalytic System for Radical Conjugate Addition of Nitrogen Heterocycles. *Chem. Sci.* **2017**, *8* (4)

[11] For other examples of photoredox catalysis in aryl radical chemistry, see: (a) Arora, A.; Weaver, J. D. Visible Light Photocatalysis for the Generation and Use of Reactive Azolyl and Polyfluoroaryl Intermediates. *Acc. Chem. Res.* **2016**, *49* (10), 2273–2283. (b) Ghosh, I.; Marzo, L.; Das, A.; Shaikh, R.; König, B. Visible Light Mediated Photoredox Catalytic Arylation Reactions. *Acc. Chem. Res.* **2016**, *49* (8), 1566–1577. (c) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. Engaging Unactivated Alkyl, Alkenyl and Aryl Iodides in Visible-Light-Mediated Free Radical Reactions. *Nat. Chem.* **2012**, *4* (10), 854–859. (d) Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; De Alaniz, J. R. A Highly Reducing Metal-Free Photoredox Catalyst: Design and Application in Radical Dehalogenations. *Chem. Commun.* **2015**, *51* (58), 11705–11708.

questioned whether this approach could be translated to heteroaryl amino acid synthesis through radical conjugate addition to dehydroalanine derivatives. There are a number of powerful methods for the synthesis of unnatural β-heteroaryl α-amino acids, including malonate (or enolate) alkylation,[12] cross-coupling of serine-derived organometallic reagents,[13] and reduction of dehydroamino acid derivatives.[14] However, strategies based on radical addition to DHA derivatives are unique due to the highly-chemoselective nature of radical species, and the broad functional group tolerance that results.[15] Alkyl radical addition to DHA has been effectively accomplished even in the complex setting of intact proteins.[16] While this is a highly attractive attribute, a radical approach to heteroaryl amino acids is currently unknown. Here, we describe the successful translation of our reductive heteroarene activation system to amino acid synthesis.

3.3 Results and discussion

Illustrated in Figure 3.2 is a mechanistic picture that is consistent with our observations. Excitation of the photocatalyst $[Ir(ppy)_2(dtbbpy)]PF_6$ ($[Ir]^{1+}$), followed by reductive quenching of the excited

[12] (a) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. Development and Applications of Amino Acid Derived Organometallics. *Synlett* **2005**, No. 18, 2701–2719. (b) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. Alkylation of Amion Acids without Loss of the Optical Activity: Preparation of Alpha-Substituted Proline Derivitives, A Case of Self-Reproduction of Chirality. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398. (c) Kolar, P.; Petric, A.; Tisler, M. Heteroarylalanines. *J. Heterocycl. Chem.* **1997**, *34*, 1067–1098.

[13] (a) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. Development and Applications of Amino Acid Derived Organometallics. *Synlett* **2005**, No. 18, 2701–2719. (b) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; Dibenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *138* (15), 5016–5019. (c) Lu, X.; Yi, J.; Zhang, Z. Q.; Dai, J. J.; Liu, J. H.; Xiao, B.; Fu, Y.; Liu, L. Expedient Synthesis of Chiral α-Amino Acids through Nickel-Catalyzed Reductive Cross-Coupling. *Chem. - A Eur. J.* **2014**, *20* (47), 15339–15343

[14] (a) Kreuzfeld, H. J.; Döbler, C.; Schmidt, U.; Krause, H. W. Synthesis of Non-Proteinogenic (D)- or (L)-Amino Acids by Asymmetric Hydrogenation. *Amino Acids* **1996**, *11* (3–4), 269–282. (b) Adamczyk, M.; Akireddy, S. R.; Reddy, R. E. Enantioselective Synthesis of (2-Pyridyl)Alanines via Catalytic Hydrogenation and Application to the Synthesis of L-Azatyrosine. *Org. Lett.* **2001**, *3* (20), 3157–3159. (c) Kreuzfeld, H. J.; Döbler, C.; Schmidt, U.; Krause, H. W. Synthesis of Non-Proteinogenic (D)- or (L)-Amino Acids by Asymmetric Hydrogenation. *Amino Acids* **1996**, *11* (3–4), 269–282.

[15] Deska, J. in *Radical-Mediated synthesis of α-Amino Acids and Peptides, in Amino Acids, Peptides and Proteins in Organic Chemistry: Building Blocks, Catalysis and Coupling*, **2010**, vol. 3.

[16] (a) Wright, T. H.; Bower, B. J.; Chalker, J. M.; Bernardes, G. J. L.; Wiewiora, R.; Ng, W. L.; Raj, R.; Faulkner, S.; Vallée, M. R. J.; Phanumartwiwath, A.; Coleman, O. D.; Thézénas, M. L.; Khan, M.; Galan, S. R. G.; Lercher, L.; Schombs, M. W.; Gerstberger, S.; Palm-Espling, M. E.; Baldwin, A. J.; Kessler, B. M.; Claridge, T. D. W.; Mohammed, S.; Davis, B. G. Posttranslational Mutagenesis: A Chemical Strategy for Exploring Protein Side-Chain Diversity. *Science (80-.).* **2016**, *354* (6312), aag1465-1–11. (b) Yang, A.; Ha, S.; Ahn, J.; Kim, R.; Kim, S.; Lee, Y.; Kim, J.; Söll, D.; Lee, H. Y.; Park, H. S. A Chemical Biology Route to Site-Specific Authentic Protein Modifications. *Science (80-.).* **2016**, *354* (6312), 623–626.

state by Hantzsch ester (HEH) gives rise to the $[Ir]^0$ ($E_{1/2}$ = −1.51 V).[17] Stern–Volmer quenching studies indicated that Hantzsch ester is the most significant excited state quencher. Single electron

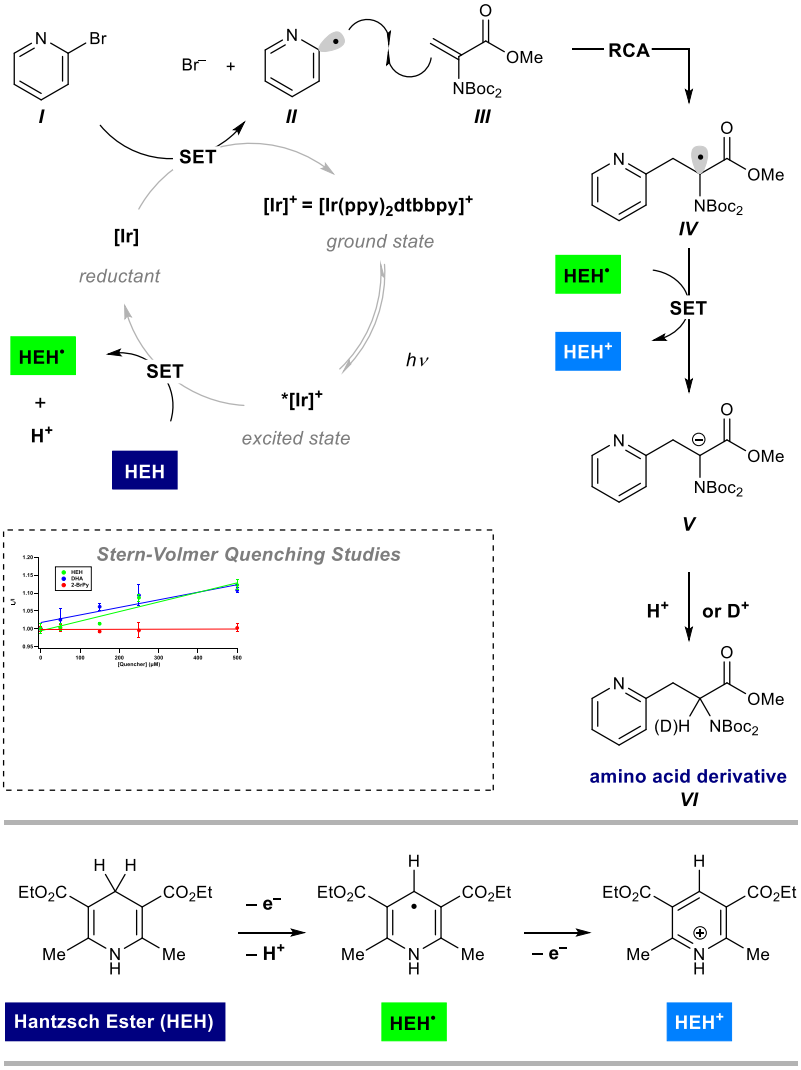


Figure 3.2. A proposed mechanism of heteroaryl radical conjugate addition to Dha.

[17] (a) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R. Pascal Jr., R. A.; Milliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater*. **2005**, *17*, 5712–5719.

reduction of halo pyridine **I**, followed by rapid mesolytic cleavage in polar solvents (X = Br, I)[18] affords heteroaryl radical intermediate **II**, which exhibits nucleophilic radical behavior in aqueous DMSO.[10a] It is possible that halopyridine reduction is assisted by protonation, as each catalytic turnover produces an nominal equivalent of Hantzsch pyridinium bromide (HEH^+ Br^-). Hydrodehalogenation (HDH) of the arene is observed as a common byproduct, but this undesired pathway can be suppressed by limiting the solubility of the stoichiometric reductant, Hantzsch ester (HEH), in accord with our previous findings. Radical conjugate addition (RCA) to dehydroalanine **III** and subsequent single electron reduction of the nascent radical **IV** would deliver the corresponding enolate **V**. The intermediacy of **V** is supported by the fact that the α-H amino acid product **VI** is produced in the presence of H_2O as a cosolvent (regardless of H/D labeling of HEH). Conversely, when D_2O is used as a cosolvent, complete deuterium incorporation is obtained at the α-position. As illustrated in Table 3.1, we identified conditions that efficiently

unite 2-bromo-5-hydroxypyridine with the indicated dehydroalanine derivative (readily accessed on 35 g scale from Boc-Ser-OMe) to give the protected azatyrosine **1** in 98% NMR yield (entry 1). These conditions employ 1 mol% of the photosensitizer $[Ir(ppy)_2(dtbbpy)]PF_6$ (excited by irradiation with a commercial blue LED) and Hantzsch ester (1.5 equiv.) as a stoichiometric reductant in aqueous DMSO. Control experiments indicated that all of these components are necessary for the reaction (entries 2–4, 0% yield), and that use of the prototypical $Ru(bpy)_3^{2+}$ chromophore results in product formation, although with diminished efficiency (entry 5, 58% yield). Omission of water as a cosolvent was not well tolerated here (entry 6, 14% yield), a finding

[18] (a) Andrieux, C. P.; Blocman, C.; Dumas-Bouchiat, J. M.; Saveant, J. M. Heterogeneous and Homogeneous Electron Transfers to Aromatic Halides. An Electrochemical Redox Catalysis Study in the Halobenzene and Halopyridine Series. *J. Am. Chem. Soc.* **1979**, *101* (13), 3431–3441. (b) Enemærke, R. J.; Christensen, T. B.; Jensen, H.; Daasbjerg, K. Application of a New Kinetic Method in the Investigation of Cleavage Reactions of Haloaromatic Radical Anions. *J. Chem. Soc. Perkin Trans. 2* **2001**, No. 9, 1620–1630

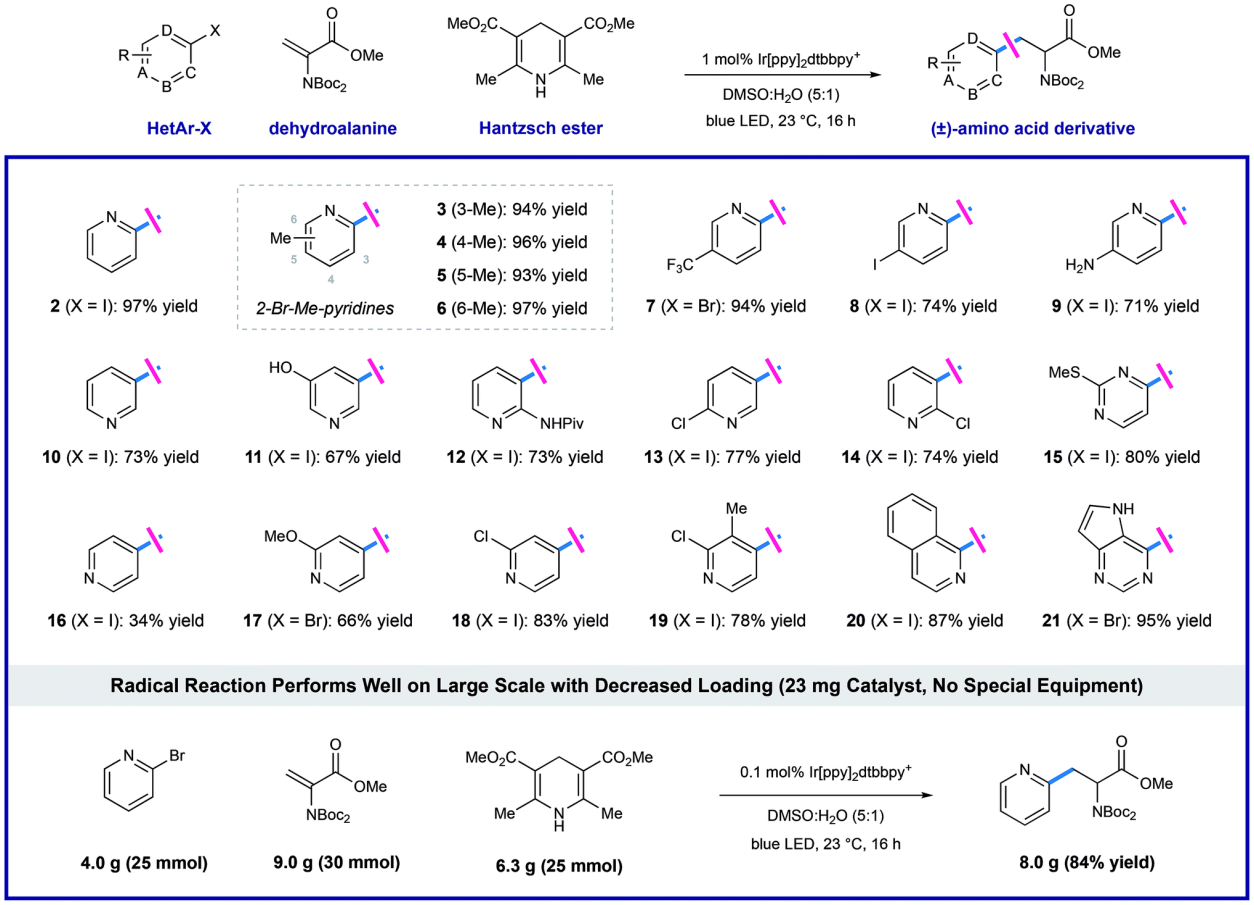
Table 3.1. Optimal conditions for pyridyl radical addition to dehydroalanine substrate

bromopyridine **dehydroalanine** **protected azatyrosine (1)**

Entry	Deviation from Optimal Conditions	Yield of 1[b]
1	none	**98%**
2	without Hantzsch ester	**0%**
3	without light	**0%**
4	without catalyst	**0%**
5	$Ru(bpy)_3Cl_2$ as catalyst	**58%**
6	without H_2O	**14%**
7	DMF:H_2O (5:1) as solvent	**35%**
8	EtOH:H_2O (5:1) as solvent	**71%**
9	bourbon as solvent (open to air)	**93%**

that is in consistent with our previous observations.[10a] We found that other aqueous solvent mixtures can be used (entries 7 and 8, 35% and 71% yield, respectively), and that this photoredox system is remarkably robust; an experiment using bourbon as solvent (open to air) afforded the desired product in 93% yield (entry 9). Importantly, protection of the phenol O–H function was not required under these mild radical conditions. Using the optimized protocol outlined above, we found that the heteroaryl halide scope of this transformation is broad (as shown in Table 3.2). Some reactions are complete in as little as 2 hours, but each experiment was conducted overnight (16 h) for consistency and convenience without negatively impacting the yields. Regiospecific activation of each pyridyl position is possible *via* single electron reduction, and these conditions effectively delivered amino ester products from 2- and 3-iodopyridine (**2** and **10**), in 97% and 73% yield, respectively. Although less efficient, 4-iodopyridine also affords 4-pyridylalanine in useful yield (**16**, 34% yield), where reductive pyridine production is a significant alternative pathway.

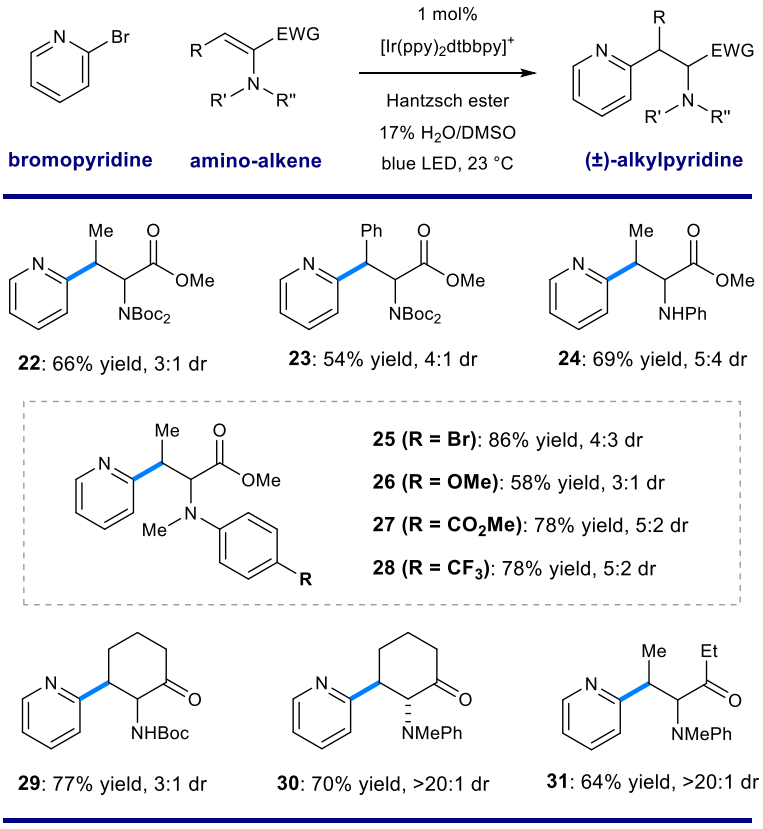
Table 3.2. Catalytic amino acid synthesis: scope of the halogenated heteroarene



Methyl substitution is well-tolerated at all positions of 2-bromo pyridines, cleanly furnishing the corresponding pyridylalanines **3–6** in very high yield (93–97% yield). Reaction of 2-bromo-5-trifluoromethylpyridine (**7**) efficiently afforded product in 94% yield. Electron-donating groups are well-tolerated including amino (**9**, 71% yield), phenol (**11**, 67% yield), amide (**12**, 73% yield), and methoxy (**17**, 66% yield) groups. Dihalogenated pyridines can be programmed for regiospecific radical formation and subsequent conjugate addition at any position, preserving 2-chloro-substituents in the presence of more reactive iodo-substituents. Coupling reactions of 2-chloro-3-iodo- (**14**), 2-chloro-4-iodo-(**18**), 2-chloro-5-iodo-(**13**), and 2-chloro-3-methyl-4-

iodopyridine (**19**) each gave single pyridylalanine products in good yield (73–83% yield). 2,5-Diiodopyridine is selectively activated at the more electrophilic 2-position to afford the corresponding amino ester (**8**) as a single regioisomer in 74% yield. We found that halopyrimidines are also viable substrates in this process: 4-iodo-2-(methylthio)pyrimidine (**15**) and 4-bromodeazapurine (**21**) gave product in 80% and 95% yield respectively. This photoredox process is amenable to gram-scale preparation of heteroaryl amino acid synthesis, without the need

Table 3.3. Radical conjugate addition: scope of the amino substituted alkene



for special equipment. We reacted 25 mmol of 2-bromopyridine with a slight excess (1.2 equivalents, 30 mmol) of the dehydroalanine substrate. In the presence of 1.0 equivalent of Hantzsch ester, in the presence of 1.0 equivalent of Hantzsch ester, and only 0.1 mol% (23 mg) of the iridium photoredox catalyst, the desired pyridylalanine derivative **2** was produced in 84% yield (8.0 g) after purification. As anticipated, selective unveiling of the amine and acid groups (in compound **2**) using standard conditions went without issue. Hydrolysis of the methyl ester (2.0 equiv. of LiOH in THF/H_2O) occurred with preservation of both Boc groups. Exposure of **2** to trifluoroacetic acid in CH_2Cl_2 revealed the free amine as the TFA salt while leaving the methyl ester intact. Finally, sequential treatment of **2** with KOH in EtOH/H_2O followed by direct acidification of the reaction mixture with HCl afforded the fully deprotected 2-pyridylalanine as the double HCl salt. Each of these processes occurred in high yield at room temperature (see ESI for details). We conducted a brief evaluation of the scope of amino-substituted alkenes with the expectation that this reaction template could be flexibly utilized to deliver other amino acid or amino-carbonyl substructures. We found that dehydroamino acid substrates with methyl- and phenyl-substituents in the β-position could be successfully employed, giving rise to products **22** and **23** in acceptable yield (66% and 54% yield, respectively) with modest diastereocontrol. Replacement of the α-imide group in the alkene starting material (a structural artifact of dehydroalanine synthesis *via* Boc_2O-induced β-elimination) with an N–H aniline group or electronically diverse arylmethylamine groups was tolerated, although diastereoselectivity was low (**25–28**, 66–75% yield, ≤3 : 1 dr). These radical conjugate addition conditions directly translated to the synthesis of β-heteroaryl α-amino ketone derivatives **29–31**, giving the desired products in 64–77% yield. These results are notable because they show the ability of this mild radical system to accomplish the formation of other of α-aminocarbonyl classes.

We have demonstrated that this process is robust, scalable, and generally applicable for the synthesis of many heteroaryl amino acid and ketone derivatives. However, we recognize that the formation of products as racemic mixtures represents a main limitation of this method. To address this, we prepared the chiral *tert*-butyl oxazolidinone **32** that was described by Beckwith,[19] building on early work by Karady,[20] and Seebach.[21] In accord with early studies, we found that heteroaryl radical addition followed by diastereoselective protonation from the less hindered *Re*-face could be achieved with a variety of halo-heteroarenes, furnished *syn*-products **33–36** with complete diasterocontrol (57–80% yield, >20 : 1 dr). Concurrent carbamate cleavage and hemiaminal hydrolysis of **36** under acidic conditions cleanly afforded the amino acid **37** with retention of stereochemical purity (98% yield, 97% ee) (Table 3.4). Other reducible radical precursors can be employed without modification of the reaction conditions to afford oxazolidinone adducts as single diastereomers. For example, the reaction of allyl bromide gives oxazolidinone **39** (42% yield). A redox-active *N*-hydroxyphthalimide ester[22] reacted to give **38** in high yield (86% yield). Finally, reducible fluorinated alky halides operate within this manifold, affording oxazolidinone adducts **40–42** with good efficiency (60–93% yield). Deprotection of two of these products would directly

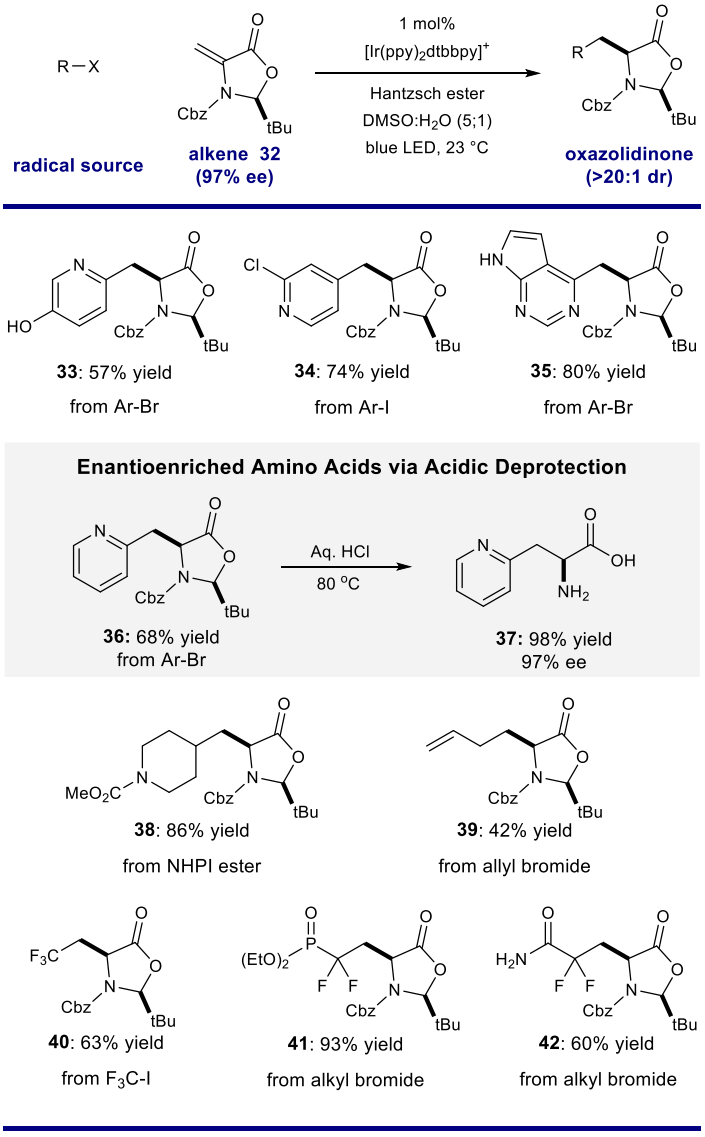
[19] Chai, C. L. L.; Beckwith, Athelstan, L. J. Diastereoselective Radical Addition to Derivatives of Dehydroalanine and of Dehydrolactic Acid. *J. Chem. Soc. Chem. Commun.* **1990**, 1087–1088.

[20] Karady, S.; Amato, J. S.; Weinstock, L. M. Enantioretentive Aalkylation of Acyclic Amino Acids. *Tetrahedron Lett.* **1984**, *25* (39), 4337–4340.

[21] Seebach, D.; Fadel, A. N,O-Acetals from Pivalaldehyde and Amino Acids for the a-Alkylation with Self-Reproduction of the Center of Chirality. Enolates of 3-Benzoyl-2-(Tert-Butyl)-1,3-Oxazolidin-5-Ones. *Helv. Chem. Acta* **1985**, *68*, 1243–1250

[22] (a) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. Photosensitized Decarboxylative MIchael Addition through N-)Alcyloxy-Phthalimides via an Electron-Transfer Mechanism. *J. Am. Chem. Soc.* **1991**, *113* (24), 9401–9402. (b) Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. Fragment Coupling and the Construction of Quaternary Carbons Using Tertiary Radicals Generated from Tert -Alkyl N -Phthalimidoyl Oxalates by Visible-Light Photocatalysis. *J. Org. Chem.* **2015**, *80* (12), 6012–6024. (c) Liu, P.; Zhao, Y.; Qin, R.; Mo, S.; Chen, G.; Gu, L.; Chevrier, D. M.; Zhang, P.; Guo, Q.; Zang, D.; Wu, B.; Fu, G.; Zheng, N. Catalysis: Photochemical Route for Synthesizing Atomically Dispersed Palladium Catalysts. *Science.* **2016**, *352* (6287), 797–801. (d) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; Dibenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *138* (15), 5016–5019.

Table 3.4. Diastereoselective RCA to Karady-Beckwith Alkene



yield fluorinated amino acids which have been enabling tools in a number of biomedical applications.[23] For example, the difluorinated phosphonate L-phosphoserine mimic (deprotected **41**) is an important tool in the study of kinase-dependent signal transduction.[23a] Because chiral

[23] (a) Panigrahi, K.; Eggen, M. J.; Maeng, J. H.; Shen, Q.; Berkowitz, D. B. The α,α-Difluorinated Phosphonate L-PSer-Analogue: An Accessible Chemical Tool for Studying Kinase- Dependent Signal Transduction. *Chem. Biol.* **2009**, *16* (9), 928–936. (b) Dave, R.; Badet, B.; Meffre, P. γ-Fluorinated Analogues of Glutamic Acid and Glutamine. *Amino Acids* **2003**, *24* (3), 245–261.

alkene **32** is easily accessible from cysteine, and both enantiomers of this starting material are commercial, this strategy would enable access to either enantiomer of the unnatural heteroaryl amino acids (Table 3.4).

3.4 Conclusions

In summary, we have described an efficient catalytic system for the preparation of unnatural α-amino acids. This protocol is effective for regiospecific generation of a broad range of heteroaryl radicals, and intermolecular coupling with dehydroamino acid derivatives and α-aminoenones. We demonstrate that this photoredox system can be conducted on large scale using near-stoichiometric conditions with good efficiency. We also show that diastereoselective radical conjugate addition to a chiral alkene is a viable strategy to access enantioenriched products, and that this process allows utilization of a range of radical precursors. The application of these findings to the synthesis of other valuable, highly complex products is a current aim of our program.

3.5 Experimental Information

3.5.1 General Information

General Reagent Information:

All reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (LEDwholesalers PAR38 Indoor Outdoor 16-Watt LED Flood Light Bulb, Blue; or PARsource PowerPAR LED Bulb-Blue 15 Watt/440 nm, available at www.eaglelight.com). Flash chromatography was carried out using Siliaflash® P60 silica gel obtained from Silicycle. Photoredox catalyst, $[Ir(ppy)_2(dtbbpy)]PF_6$, was prepared according to a literature procedure[24]. Halogenated heteroarenes were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, Combi-Blocks, or Oakwood Products and were used as received. Dehydroalanines were prepared according to the designated procedures in section IV, Preparation of Dehydroalanine Substrates. Molecular sieves were activated in a commercial microwave oven then cooled under high vacuum. DMSO was purified on a Pure Process Technologies solvent purification system. Reaction solvent was prepared by combining DMSO and tap water (5:1, V:V) which was degassed in a sidearm flask under weak vacuum while subject to sonication. Alcoholic beverages used as solvents for optimization screenings were purchased from a local package store and used as received.

[24] Lowry, M. S.; Hudson, W. R.; Pascal, R. A.; Bernhard, S. *J. Am. Chem. Soc*. **2004**, *126*, 14129.

General Analytical Information:

All yields refer to isolated yields. New compounds were characterized by NMR, IR spectroscopy, HRMS, and melting point. NMR data were recorded on one of six spectrometers: Bruker 600 MHz, INOVA 600 MHz, INOVA 500 MHz, VNMR 400 MHz, INOVA 400 MHz, or Mercury 300 MHz. Chemical shifts (δ) are internally referenced to residual protio solvent ($CDCl_3$: δ 7.26 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR; C_6D_6: 7.15 ppm for ^1H NMR and 128.4 ppm for ^{13}C NMR; CD_3OD: δ 3.31 ppm for ^1H 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 using a Thermo LTQ-FTMS high resolution mass spectrometer. Melting point data was obtained with a Thomas Hoover Unimelt capillary melting point apparatus. Adduct yields for optimization data were obtained via H^1 NMR with an Inova 400 MHz NMR using 1,3,5-trimethoxybenzene as internal standard, with relaxation delay set to 5 seconds. Hydrodehalogenated yields for optimization data were obtained via gas chromatography with an Agilent Technologies 7890B Gas Chromatography system (flame-ionization detection) equipped with an Agilent Technologies 19091J-413 HP-5 column (30 m x 0.320 mm x 0.25 µm, 5% phenyl methyl siloxane) and an Agilent Technologies G4513A autoinjector. Enantioenriched samples were analyzed on a 1100 Series Agilent HPLC on Daicel Chiralcel columns (250 x 4.6 mm ID). Optical rotations were measured at 20 °C using a Perkin Elmer Model 341 Polarimeter at λ = 589 nm.

3.5.2 General Procedure:

A 20-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (1.3 – 1.5 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%), dehydroalanine (2 equiv), and halogenated heteroarene (1 equiv). The

tube was sealed with PTFE/silicon septum and connected to a Schlenk 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 (5:1 DMSO:H_2O, 10 mL/mmol heteroarene) by syringe. The resulting suspension was stirred under irradiation with blue LEDs for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution (60 mL) and extracted with ethyl acetate (3 x 40 mL). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

3.5.3 Optimization Details

Procedure for In-Text Deviation from Optimal Conditions:

A 15-mL screw-top test tube equipped with a stir bar was charged with Hantzsch ester (76 mg, 0.30 mmol, 1.5 equiv), photoredox catalyst (1 mol%), methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (120 mg, 0.4 mmol, 2 equiv), and 2-bromopyridine (31.6 mg, 0.20 mmol, 1 equiv). The tube was sealed with PTFE/silicon septum and connected to a Schlenk 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 degassed solvent (2.0 mL) by syringe. The resulting suspension 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 scintillation vial. An internal standard of dodecane (10 µL, 0.044 mmol) was delivered to the vial, and the contents were thoroughly mixed. A sample was analyzed by gas

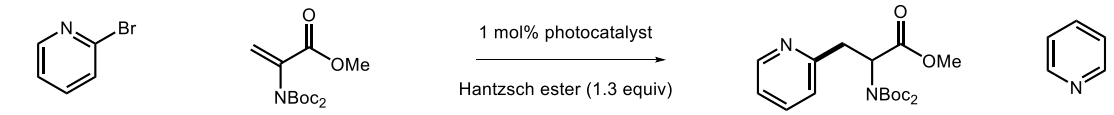
chromatography, and the integral values were used to calculate hydrodehalogenation product (pyridine) yield. The contents of the vial were concentrated via rotary evaporation and then subject to high vacuum for 2 hours. 1,3,5-trimethoxybenzene (33.6 mg, 1 equiv) was added, and the contents were thoroughly dissolved in $CDCl_3$. An aliquot was analyzed by H^1NMR, and the integral values were used to calculate pyridylalanine ester yield.

Gas Chromatography Method Conditions:

The gas chromatography system hardware is reported in section I-B, General Analytical Information. The injection volume for each trial is 0.5 µL. The initial oven temperature was set to 50 °C, and the ramp rate was programmed to 20 °C/min until reaching 150 °C. With no hold time, the temperature ramp rate is adjusted to 25 °C/min until reaching the maximum temperature of 325 °C. Maximum temperature is held for one minute before concluding the run.

Optimization Table

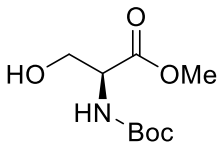
Table S3.1. Optimization of heteroaryl RCA to Dha



2-bromopyridine **DHA (2.0 equiv)** **(±)-A** **B**

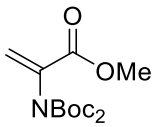
entry	photocatalyst	solvent	deviation	% yield **A**	% yield **B**	selectivity (**A:B**)
1	$Ru(bpy)_3Cl_2$	MeCN (0.1 M)	-	0	0	-
2	$Ir(ppy)_3$	MeCN (0.1 M)	-	48	2	24:1
3	$Ir(dF(CF_3)ppy)_2dtbbpy•PF_6$	MeCN (0.1 M)	-	50	2	25:1
4	$Ir(ppy)_2dtbpy•PF_6$	MeCN (0.1 M)	-	52	2	26:1
5	$Ru(bpy)_3Cl_2$	DMSO (0.1 M)	-	54	2	27:1
6	$Ir(ppy)_3$	DMSO (0.1 M)	-	65	2	33:1
7	$Ir(dF(CF_3)ppy)_2dtbbpy•PF_6$	DMSO (0.1 M)	-	81	11	7:1
8	$Ir(ppy)_2dtbbpy•PF_6$	DMSO (0.1 M)	-	81	11	7:1
9	$Ir(ppy)_2dtbbpy•PF_6$	DMF/H_2O (3:1, 0.1M)	-	34	2	17:1
10	$Ir(ppy)_2dtbbpy•PF_6$	MeCN/H_2O (3:1, 0.1M)	-	27	3	9:1
11	$Ir(ppy)_2dtbbpy•PF_6$	MeOH/H_2O (3:1, 0.1 M)	-	30	1	30:1
12	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (3:1, 0.1 M)	-	85	3	28:1
13	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (3:1, 0.03 M)	-	98	2	49:1
14	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (5:1, 0.1 M)	-	98	2	49:1
15	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (5:1, 0.1 M)	1.1 equiv DHA	93	7	13:1
16	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (5:1, 0.1 M)	air-exposed	90	5	18:1
17	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (5:1, 0.1 M)	1.1 equiv DHA, air-exposed	85	7	12:1
18	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (5:1, 0.1 M)	no Hantzsch ester	0	0	-
19	$Ir(ppy)_2dtbbpy•PF_6$	DMSO/H_2O (5:1, 0.1 M)	no light	0	0	-
20	none	DMSO/H_2O (5:1, 0.1 M)	-	0	0	-
21	$Ir(ppy)_2dtbbpy•PF_6$	Grey Goose vodka (0.033 M)	-	85	12	7:1
22	$Ir(ppy)_2dtbbpy•PF_6$	Bacardi white rum (0.033 M)	-	86	12	7:1
23	$Ir(ppy)_2dtbbpy•PF_6$	Johnnie Walker Scotch (0.033 M)	-	84	12	7:1
24	$Ir(ppy)_2dtbbpy•PF_6$	Woodford Reserve bourbon (0.033 M)	-	93	4	23:1
25	$Ir(ppy)_2dtbbpy•PF_6$	Seagram's gin (0.033 M)	-	94	4	24:1
26	$Ir(ppy)_2dtbbpy•PF_6$	Redbull/Grey Goose (1:2, 0.033 M)	-	42	1	42:1

3.5.4 Preparation of Dehydroalanine Substrates:



methyl (*tert*-butoxycarbonyl)-L-serinate:

To a stirring solution of L-serine, methyl ester hydrochloride (20.0g, 128 mmol, 1 equiv) in dichloromethane (130 mL) at 0 °C was added triethylamine (40 mL, 282 mmol, 2.2 equiv) and di-*tert*-butyl dicarbonate (37 mL, 135 mmol, 1.1 equiv). After stirring for 30 minutes, the solution was warmed to room temperature, and stirred for an additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The reside was passed through a silica plug (50% ethyl acetate in hexanes) to afford the product as a clear, colorless oil (37.2 g 94% yield). The physical properties and spectral data are consistent with the reported values.[25]

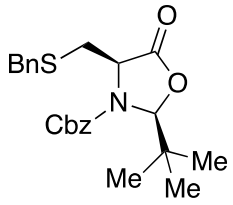


methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate:

To a stirring solution of methyl (*tert*-butoxycarbonyl)-L-serinate (37.2, 120 mmol, 1.0 equiv) in acetonitrile (200 mL) at 0 °C was added di-*tert*-butyl dicarbonate (58.3 mL, 281 mmol, 2.2 equiv)

[25] Hiroaki, T. and Hisashi, Y. *J. Am. Chem. Soc.* **2016**, *138*, 14218.

and 4-dimethylaminopyridine (3. 12 g, 25.6 mmol, 0.20 equiv). The resulting solution was warmed to room temperature and stirred for 8 hours. DBU (2.00 g, 12.8 mmol, 0.10 equiv) was added, and the resulting mixture was stirred for an additional 8 hours. The reaction was concentrated by rotary evaporation then diluted in ethyl acetate. The mixture was washed with 1M HCl and saturated aqueous $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by passing through a short plug of silica (5% – 15% ethyl acetate/hexanes) to afford the product (31.5 g, 89% yield) as a white solid. The physical properties and spectral data are consistent with the reported values.[26]



benzyl (2*S*,4*R*)-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 or until nearly homogenous. Pivaldehyde (4.9 g, 57 mmol, 1.2 equiv) and activated 3 Å molecular sieves (50 g) 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 ^{1}H NMR of a filtered and concentrated aliquot of the reaction solution dissolved in D_3COD). The reaction was quickly

[26] Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; and Winn, C. L. *J. Org. Chem.* **2003**, *68*, 9433.

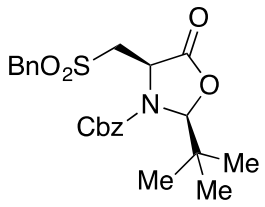
filtered through celite and concentrated by rotary evaporation. The residue was dried under high vacuum for 4 hours to afford the imine as a white solid. The imine was dissolved in anhydrous DCM (500 mL) and cooled to 0 °C in an oversized, well-insulated ice bath. Benzyl chloroformate (10.1 mL, 71 mmol, 1.5 equiv) was added to the cooled reaction dropwise via syringe. The reaction was stirred at 0 °C 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 (1 x 250 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (5% – 15% ethyl acetate/hexanes) to afford the product (8.2 g, 42% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 5H), 7.33 – 7.20 (m, 5H), 5.55 (s, 2H), 5.21 (dd, *J* = 16.6, 12.1 Hz, 2H), 4.55 (dd, *J* = 7.8, 6.2 Hz, 1H), 3.78 (q, *J* = 13.4 Hz, 1H), 2.94 (dd, *J* = 13.9, 8.0 Hz, 1H), 2.79 (dd, *J* = 13.9, 6.1 Hz, 1H) 0.93 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.15, 155.69, 137.65, 135.06, 128.96, 128.58, 128.43, 128.38, 127.00, 96.12, 68.36, 57.44, 36.77, 36.36, 33.19, 24.72.

FTIR (neat) ν_{max}: 33063, 3031, 2970, 1791, 1717, 1481, 1454, 1390, 1344, 1324, 1221, 1196, 1170, 1118, 1036, 1016, 968, 908, 728, and 697 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{28}O_4NS$, 414.17336; found, 414.17310.



benzyl (2*S*,4*R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxy-late:

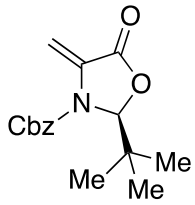
To a round bottom flask equipped with a stir bar was added benzyl (2*S*,4*R*)-4-((benzylthio)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate (2.4 g, 6 mmol, 1 equiv), *meta*-chloroperoxybenzoic acid (2.5 g, 15 mmol, 2.5 equiv), and DCM (200 mL). The reaction was stirred at room temperature for 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 (5% – 30% ethyl acetate/hexanes) to afford the product (2.5 g, 95% yield) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.22 (m, 10H), 5.60 (s, 1H), 5.30 – 5.14 (m, 2H), 5.07 (dd, *J* = 7.9, 4.0 Hz, 1H), 4.63 (d, *J* = 14.0 Hz, 1H), 4.40 (d, *J* = 14.0 Hz, 1H), 3.42 (dd, *J* = 15.3, 7.9 Hz, 1H), 3.15 (dd, *J* = 15.3, 4.0 Hz, 1H), 0.87 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.75, 155.31, 134.91, 129.07, 128.99, 128.77, 128.72, 128.70, 127.90, 96.83, 68.82, 60.25, 53.59, 52.65, 37.05, 24.53.

FTIR (neat) ν_{max}: 3066, 3034, 2972, 2874, 2256, 1791, 1719, 1456, 1392, 1312, 1285, 1119, 1039, 966, 908, 725, and 696 cm^{-1}.

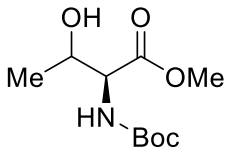
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{24}O_2N_5S$, 446.16452; found, 446.16398.



benzyl (*S*)-2-(*tert*-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (22):

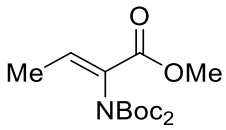
To a round bottom flask equipped with a stir bar was added (benzyl (2*S*,4*R*)-4-((benzylsulfonyl)methyl)-2-(*tert*-butyl)-5-oxooxazolidine-3-carboxylate) (3.6g, 8 mmol, 1 equiv), and DCM (100 mL). The flask was chilled to 0 °C in an ice bath, and DBU (1.3 mL, 9 mmol, 1.1 equiv) was added dropwise via 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 (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 (5% – 15% ethyl acetate/ hexanes) to afford the product (2.0 g, 87% yield) as a colorless oil. The physical properties and spectral data are consistent with the reported values[27]. Chiral HPLC analysis of the alkene (OJ-H, 5% IPA/hexanes, 1.0 mL/min, 254 nm) indicated 97% ee for the major enantiomer (t_R (minor) = 11.800 min, t_R (major) = 13.225 min).

[27] Hargrave, J. D.; Bish, D.; Köhn, G. K.; and Frost, C. G *Org. Biomol. Chem.*, **2010**, *8*, 5120.



methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanoate:

To a stirring solution of L-threonine, methyl ester hydrochloride (8.2 g, 49 mmol, 1.0 equiv) in dichloromethane (80 mL) at 0 °C was added triethylamine (21 mL, 150 mmol, 3.0 equiv) and di-*tert*-butyl dicarbonate (12 g, 53 mmol, 1.1 equiv). After stirring 30 minutes, the solution was warmed to room temperature, and stirring was continued for an additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was passed through a silica plug to afford the product (10.7 g, 95% yield) as a clear, colorless oil. The physical properties and spectral data are consistent with the reported values.[2]



methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate:

To a stirring solution of methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanoate

(10.0 g, 42.9 mmol, 1.0 equiv) in acetonitrile (120 mL) at 0 °C was added di-*tert*-butyl dicarbonate (19.6 g, 90.1 mmol, 2.1 equiv) and DMAP (510 mg, 4.2 mmol, 0.10 equiv). The resulting solution was warmed to room temperature, and after stirring for 8 hours DBU (1.31 g, 8.59 mmol, 0.20 equiv) was added, and the resulting mixture was stirred for 8 hours. The reaction was concentrated

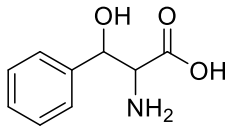
by rotary evaporation then diluted in ethyl acetate. The mixture was washed with 1M HCl and saturated aqueous $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by passing through a short pad of silica (hexane/ethyl acetate = 30%) to afford the product (9.59 g, 71% yield) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 – 6.68 (m, 1H), 3.72 (s, 3H), 1.72 (d, *J* = 7.1 Hz, 2H), 1.41 (d, *J* = 1.0 Hz, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.34, 150.41, 136.58, 130.18, 82.70, 52.06, 27.82, 13.31.

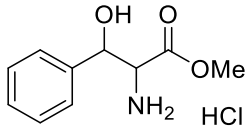
FTIR (neat) ν_{max}: 2980, 2953, 2935, 1792, 1757, 1727, 1368, 1270, 1250, 1152, 1093, 1044, and 730 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{26}NO_6$, 316.17546; found, 316.17564.



2-amino-3-hydroxy-3-phenylpropanoic acid:

To a stirring solution of NaOH (10 g, 250 mmol, 4.5 equiv) in water (50 mL) was added glycine (5.7 mL, 56 mmol, 1.0 equiv). The solution was stirred 10 minutes, then benzaldehyde (10 g, 151 mmol, 2.9 equiv) was added. The solution was stirred for an additional 30 minutes as an off-white emulsion formed. The precipitant was broken apart in the flask, and concentrated HCl (aq) (130 mL) was added slowly while stirring until consumption of the solid was observed to give a clear yellow solution. After stirring an additional 10 minutes, a beige precipitate formed. The reaction mixture was cooled to 0 °C, and the precipitate was collected by vacuum filtration and washed with ether. The solid was dried under high vacuum to give the product as an off-white solid (11.6 g, 72% yield). The physical properties and spectral data are consistent with the reported values.[28]

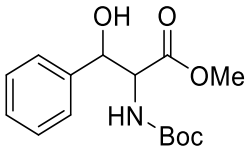


methyl (2S)-2-amino-3-hydroxy-3-phenylpropanoate:

To a stirring solution of 3-hydroxyphenylalanine (3.62 g, 20 mmol, 1.0 equiv) in methanol (80 mL) at 0 °C was added thionyl chloride (3.5 g, 30 mmol, 1.5 equiv) dropwise via syringe, and the reaction mixture was stirred for 30 minutes while gradually warming to room temperature. Upon

[28] Shiraiwa, T.; Saijoh, R.; Suzuki, M.; Yoshida, K.; Nishimura, S.; Nagasawa, H. *Chem. Pharm. Bull.* **2003**, *51*, 1363.

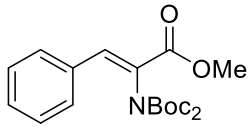
reaching room temperature, a reflux condenser was attached, and the reaction mixture was heated to 65 °C and stirred under reflux for an additional 5 hours. After cooling to room temperature, the reaction mixture was concentrated by rotary evaporation, diluted with chloroform, concentrated by rotary evaporation, washed with ether, and dried under high vacuum for 2 hours to afford the product as a white solid (4.6 g, 99% yield). The physical properties and spectral data are consistent with the reported values.[29]



phenylalanine, *N*-[(1,1-dimethylethoxy)carbonyl]-β-hydroxy-, methyl ester:

To a stirring solution of methyl (2S)-2-amino-3-hydroxy-3-phenylpropanoate hydrochloride (5.8 g, 25 mmol, 1.0 equiv) in dichloromethane (70 mL) at 0 °C was added triethylamine (7.6 mL, 57 mmol, 2.5 equiv) and di-*tert*-butyl dicarbonate (5.5 mL, 25 mmol, 1.0 equiv). After stirring 30 minutes, the solution was warmed to room temperature, and stirred for an additional 18 hours. The reaction mixture was concentrated by rotary evaporation, diluted with ethyl acetate, and washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The reside was passed through a silica plug (50% ethyl acetate/hexanes) to afford the product as a clear, colorless oil (5.10 g 91% yield). The physical properties and spectral data are consistent with the reported values.[30]

[29] Miyata, O.; Asai, H.; Naito, T. *Chem. Pharm. Bull.* **2005**, *53*, 355.
[30] Bengtsson, C.; Nelander, H.; Almqvist, F. *Chem. Eur. J.*, **2013**, *19*, 9916.



methyl 2-(di(tert-butoxycarbonyl)amino)-3-phenylacrylate:

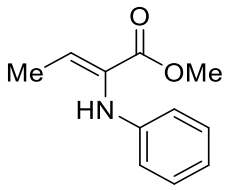
To a stirring solution of phenylalanine, *N*-[(1,1-dimethylethoxy)carbonyl]-β-hydroxy-, methyl ester (5.01 g, 16.9 mmol, 1.0 equiv) in acetonitrile (22 mL) at 0 °C was added di-*tert*-butyl dicarbonate (8.10 g, 37.2 mmol, 2.2 equiv) and DMAP (206 mg, 1.69 mmol, 0.10 equiv). The resulting solution was warmed to room temperature, and after stirring for 8 hours DBU (516 mg, 3.4 mmol, 0.2 equiv) was added, and the resulting mixture was allowed to continue stirring for an additional 8 hours. The reaction was concentrated by rotary evaporation then diluted with ethyl acetate. The organic layer was washed with 1M HCl and saturated aqueous $NaHCO_3$, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5% – 15% ethyl acetate/hexanes) to afford the product, (5.17 g, 81% yield) as a clear, colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.50 – 7.45 (m, 2H), 7.40 – 7.35 (m, 3H), 3.83 (s, 3H), 1.30 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.41, 150.02, 135.72, 133.03, 129.99, 129.60, 128.94, 127.19, 82.99, 52.46, 27.66.

FTIR (neat) ν_{max}: 2979, 2952, 2934, 1794, 1752, 1722, 1393, 1317, 1248, 1149, 1113, 1093, 1027, 850, and 780 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{24}N_2O_2$, 378.19245; found, 378.19192.



methyl 2-(phenylamino)but-2-enoate:

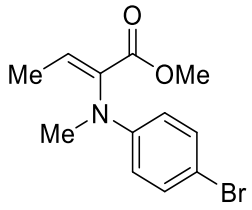
To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (6.1 g, 52 mmol, 1.0 equiv), aniline (4.8 g, 52 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (494 mg, 2.6 mmol, 0.05 equiv), and benzene (150 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 ºC while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 50% ethyl acetate/hexanes) to afford the product (6.0 g, 59% yield) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 2H), 6.86 (t, J = 7.5 Hz, 1H), 6.78 – 6.43 (m, 3H), 5.64 (s, 1H), 3.79 (s, 3H), 1.73 (d, J = 7.3 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.37, 144.24, 130.33, 129.03, 119.45, 115.35, 52.29, 14.55.

FTIR (neat) ν_{max}: 3375, 3053, 3026, 2971, 2951, 1708, 1647, 1599, 1497, 1434, 1266, 1244, 1175, 747, and 693 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{11}H_{14}O_2N$, 192.10191; found, 192.10.188.



methyl 2-((4-bromophenyl)(methyl)amino)but-2-enoate:

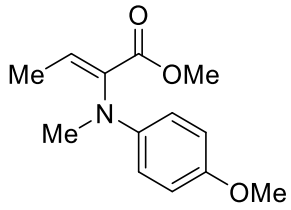
To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 2.0 equiv), 4-bromo-*N*-methylaniline (1.1 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (95 mg, 0.50 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 30% ethyl acetate/hexanes) to afford the product (1.6 g, 83% yield) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 2H), 6.99 (q, J = 7.0 Hz, 1H), 6.49 (d, J = 9.0 Hz, 2H), 3.68 (d, J = 0.9 Hz, 3H), 3.04 (s, 3H), 1.81 – 1.70 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.66, 146.95, 138.29, 136.73, 131.79, 113.92, 109.52, 51.98, 38.08, 13.51.

FTIR (neat) ν_{max}: 2972, 2950, 2819, 1732, 1589, 1498, 1434, 1371, 1303, 1239, 1206, 808, and 747cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{12}H_{15}O_2NBr$, 284.02807; found, 284.02850.



methyl 2-((4-methoxyphenyl)(methyl)amino)but-2-enoate:

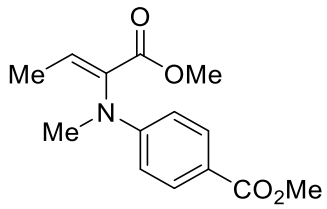
To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 2.0 equiv), 4-methoxy-*N*-methylaniline (1.4 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid (95 mg, 0.50 mmol, 0.05equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 ºC while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (1.6 g, 68% yield) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (q, J = 7.1 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.1 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 3.05 (s, 3H), 1.79 (d, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 166.26, 151.97, 142.40, 137.65, 136.99, 114.72, 113.36, 55.69, 51.79, 38.31, 13.47.

FTIR (neat) ν_{max}: 2992, 2948, 2906, 2832, 1718, 1647, 1507, 1238, 1201, 1123, 1114, 1036, and 817 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{13}H_{18}O_3N$, 236.12812; found, 236.12783.



methyl 4-((1-methoxy-1-oxobut-2-en-2-yl)(methyl)amino)benzoate:

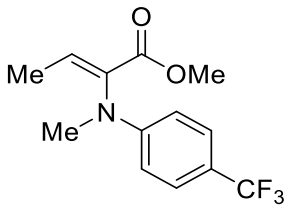
To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 1.0 equiv), methyl 4-(methylamino)benzoate (3.3 g, 20 mmol, 1.0 equiv), *p*-toluenesulfonic acid (190 mg, 1.0 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 50% ethyl acetate/hexanes) to afford the product (4.1 g, 77% yield) as a clear, colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2H), 7.02 (q, J = 6.8 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 3.81 (s, 4H), 3.66 (s, 3H), 3.08 (s, 3H), 1.72 (d, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.19, 165.27, 151.43, 138.75, 136.28, 131.27, 118.68, 111.29, 52.02, 51.45, 38.01, 13.50.

FTIR (neat) ν_{max}: 2990, 2949, 2907, 1705, 1601, 1516, 1433, 1275, 1255, 1177, 1108, 1042, and 768 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{14}H_{18}O_4N$, 264.12303; found, 264.12269.



methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)but-2-enoate:

To a round-bottom flask equipped with stir bar was added methyl 2-oxobutanoate (2.3 g, 20 mmol, 2.0 equiv), 4-trifluoromethyl-*N*-methylaniline (1.8 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 ºC while stirring for 24 hours. The reaction mixture was concentrated by rotary evaporation, and the residue was purified by flash column chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (2.3 g, 84% yield) as a clear, colorless oil.

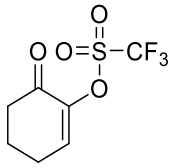
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 9.1 Hz, 1H), 7.07 (q, J = 7.0 Hz, 0H), 6.65 (d, J = 8.9 Hz, 1H), 3.71 (s, 1H), 3.10 (s, 1H), 1.76 (d, J = 7.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.39, 150.24, 139.02, 136.28, 126.57 (q, J = 4.2 Hz), 125.03 (q, J = 270.0 Hz), 118.70 (q, J = 33.1 Hz), 111.54, 52.07, 38.01, 13.49.

^{19}F NMR (282 MHz, $CDCl_3$) δ -61.01.

FTIR (neat) ν_{max}: 2994, 2953, 2912, 2825, 1720, 1650, 1613, 1524, 1321, 1257, 1205, 1193, 1102, 1067, 1043, 849, and 576 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{13}H_{15}O_2NF_3$, 274.10494; found, 274.10501.



6-oxocyclohex-1-en-1-yl trifluoromethanesulfonate:

To a stirring solution of 1,2-cyclohexanedione (5.0 g, 45 mmol, 1.0 equiv) in dichlormethane (100 mL) at -78 °C was added triethylamine (5.5 g, 54 mmol, 1.2 equiv) and trifluoromethanesulfonic anhydride (12.7 g, 45 mmol, 1.0 equiv). The resulting solution was warmed to room temperature and stirred for an additional 3 hours. The reaction was concentrated by rotary evaporation then diluted with ethyl acetate. The organic layer was washed with 1M HCl and saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (10% – 30% ethyl acetate/hexanes) to afford the product (6.2 g, 57% yield) as a white crystalline, low-melting solid.

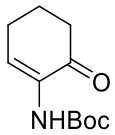
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93 (t, J = 4.4 Hz, 1H), 2.84 – 2.34 (m, 4H), 2.07 (p, J = 7.4, 6.9, 5.6, 5.6 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 189.87, 144.53, 139.55, 118.53 (q, J = 320.1 Hz), 37.69, 24.99, 21.88.

^{19}F NMR (282 MHz, $CDCl_3$) δ -73.99.

FTIR (neat) ν_{max}: 2953, 1702, 1419, 1349, 1202, 1137, 1070, 914, and 809 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_7H_8O_4S$, 245.00899; found, 245.00866.



tert-butyl (6-oxocyclohex-1-en-1-yl)carbamate:

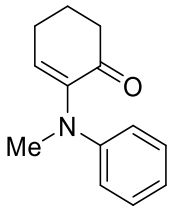
A three-neck round-bottom flask equipped with a stir bar was charged with 6-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (4.0 g, 16.3 mmol, 1.0 equiv), tert-butyl carbamate (2.2 g, 19.6 mmol, 1.2 equiv, $Pd_2(dba)_3$ (372 mg, 0.41 mmol, 0.025 equiv), 2-di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl (691 mg, 1.6 mmol, 0.10 equiv), and K_2CO_3 (5.5 g, 40.8 mmol, 2.5 equiv). A reflux condenser was connected, and each inlet was sealed with a rubber septum. 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 toluene (40 mL). The reaction mixture was heated to 80 °C and stirred under N_2 for 12 hours. After cooling to room temperature, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (10% – 70% ethyl acetate/hexanes) to afford the product (2.8 g, 80% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 4.7 Hz, 1H), 7.05 (s, 1H), 2.56 – 2.28 (m, 4H), 2.00 – 1.76 (m, 2H), 1.39 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) 193.77, 152.85, 132.41, 127.22, 80.15, 37.06, 28.16, 24.52, 22.40.

FTIR (neat) ν_{max}: 3402, 2977, 2933, 2871, 2832, 1784, 1721, 1672, 1638, 1507, 1355, 1227, 1151, 1042, 1020, 877, and 867 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{11}H_{18}O_3N$, 212.12812; found, 212.12789.



2-(methyl(phenyl)amino)cyclohex-2-en-1-one:

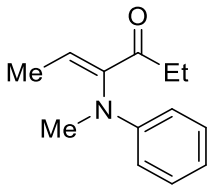
To a round-bottom flask equipped with stir bar was added cyclohexane-1,2-dione (2.2 g, 20 mmol, 2.0 equiv), *N*-methylaniline (1.1 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid (95 mg, 0.5 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 24 hours. The reaction mixture was diluted with ethyl acetate, washed with water (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5% – 30% ethyl acetate/hexanes) to afford the product (1.5 g, 80% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, J = 8.7, 7.2 Hz, 2H), 6.83 – 6.76 (m, 2H), 6.75 – 6.68 (m, 2H), 3.07 (s, 3H), 2.54 (qd, J = 6.3, 3.8 Hz, 4H), 2.09 (p, J = 6.2 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.49, 149.02, 144.65, 143.16, 128.88, 118.43, 114.79, 39.50, 39.39, 26.01, 22.95.

FTIR (neat) ν_{max}: 3058, 3024, 2942, 2874, 2813, 1680, 1596, 1497, 1323, 1128, and 747 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{13}H_{16}ON$, 202.12264; found, 202.12252.



4-(methyl(phenyl)amino)hex-4-en-3-one:

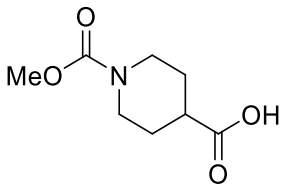
To a round-bottom flask equipped with stir bar was added hexane-3,4-dione (5.5 g, 50 mmol, 5.0 equiv), *N*-methylaniline (1.1 g, 10 mmol, 1.0 equiv), *p*-toluenesulfonic acid (95 mg, 0.5 mmol, 0.05 equiv), and benzene (50 mL). A Dean-Stark apparatus and reflux condenser were attached, and the mixture was heated to 95 °C while stirring for 18 hours. The reaction mixture was diluted with ethyl acetate, washed with water (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (5% – 30% ethyl acetate/hexanes) to afford the product (1.8 g, 91% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.16 (m, 2H), 6.88 – 6.80 (m, 1H), 6.75 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.60 (dd, *J* = 7.7, 1.1 Hz, 2H), 3.13 (s, 3H), 2.44 (q, *J* = 7.1 Hz, 2H), 1.75 (d, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 201.51, 147.56, 145.05, 135.02, 129.34, 117.32, 111.90, 38.15, 31.82, 13.61, 7.92.

FTIR (neat) ν_{max}: 3060, 2972, 2935, 2917, 1713, 1593, 1503, 1360, 746, and 691 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{13}H_{18}ON$, 204.13829; found, 204.13814.



1-(methoxycarbonyl)piperidine-4-carboxylic acid:

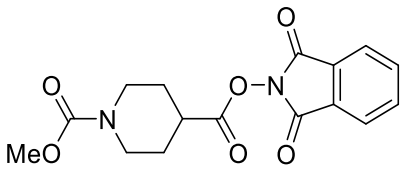
To a round bottom flask equipped with a stir bar was added piperidine-4-carboxylic acid (5.0 g, 39 mmol, 1 equiv), THF (100 mL), and saturated aqueous sodium bicarbonate (100 mL). Methyl chloroformate (6.0 mL, 77.0 mmol, 2 equiv) was then added dropwise via syringe. The reaction was allowed to stir at room temperature overnight. The reaction mixture was filtered over celite then concentrated to remove THF. The remaining solution was acidified to pH = 2 using 1 M HCl then extracted with ethyl acetate (3 x 100 mL). The combined extracts were dried over sodium sulfate, filtered, then concentrated by rotary evaporation. The residue was purified by flash chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (5.65 g, 78% yield) as a white solid.

1 H NMR (500 MHz, $CDCl_3$) δ 11.46 (s, 1H), 4.01 (m, 2H), 3.65 (s, 3H), 2.89 (t, J = 11.5 Hz, 2H), 2.46 (tt, J = 10.8, 4.0 Hz, 1H), 1.88 (d, J = 11.5 Hz, 2H), 1.61 (qd, J = 11.2, 4.0 Hz, 2H).

13C NMR (125 MHz, $CDCl_3$) δ 179.6, 156.0, 52.8, 43.1, 40.6, 27.6.

FTIR (neat) νmax: 3003, 2956, 2863, 1674, 1479, 1449, 1411, 1275, 1209, 1182, 1126, 1080, 1033, 930, 758, and 730 cm-1 .

HRMS (NSI) m/z: [M+H]+ calcd. for C8H14O4N, 188.0917; found, 188.0916.



4-(1,3-dioxoisoindolin-2-yl) 1-methyl piperidine-1,4-dicarboxylate:

To a round bottom flask equipped with a stir bar was added 1- (methoxycarbonyl)piperidine-4-carboxylic acid (5.7 g, 30 mmol, 1 equiv), Nhydroxyphthalamide (4.9 g, 30 mmol, 1 equiv), DMAP (369 mg, 3 mmol, 0.1 equiv), and DCM (300 mL). DIC (4.7 mL, 30 mmol, 1 equiv) was then added dropwise via syringe. The reaction was allowed to stir at this temperature until the starting material had been consumed (determined by TLC). The reaction mixture was filtered over celite and rinsed with an additional 50 mL of DCM. The filtrate was concentrated by rotary evaporation and the residue was purified by flash chromatography (5% – 40% ethyl acetate/hexanes) to afford the product (7.52 g, 75% yield) as a white solid.

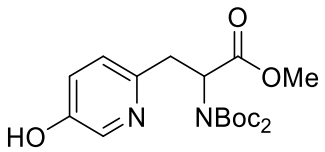
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 5.6, 3.0 Hz, 1H), 7.77 (dd, J = 5.6, 3.0 Hz, 1H), 4.13 – 3.90 (m, 1H), 3.68 (d, J = 1.4 Hz, 2H), 3.05 (t, J = 11.0 Hz, 2H), 2.91 (tt, J = 10.2, 4.0 Hz, 1H), 2.10 – 2.00 (m, 3H), 1.84 (ddt, J = 13.3, 10.2, 5.3 Hz, 3H).

13C NMR (101 MHz, $CDCl_3$) δ 170.5, 161.9, 155.8, 134.9, 128.8, 124.0, 52.7, 42.7, 38.3, 27.7.

FTIR (neat) νmax: 2956, 2863, 1813, 1785, 1754, 1694, 1468, 1448, 1411, 1373, 1316, 1276, 1233, 1186, 1128, 1076, 1000, 968, 913, 877, 786, 767, 729, 695 cm-1 .

HRMS (NSI) m/z: [M+H]+ calcd. for C16H17O6N2, 333.1081; found, 333.1081

3.5.5 Procedure and Characterization Data



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-hydroxypyridin-2-yl)propanoate (1):

Following the general procedure, the reaction of 6-bromopyridin-3-ol (174 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (608 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.4 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (361 mg, 91% yield) as an off-white solid after purification by flash column chromatography (50% – 75% ethyl acetate/hexanes).

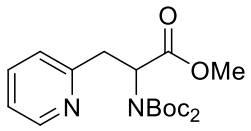
Mp: 163 °C (decomp.)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.13 (d, J = 2.9 Hz, 1H), 7.15 (dd, J = 8.5, 2.8 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 5.29 (dd, J = 10.2, 4.8 Hz, 1H), 3.69 (s, 3H), 3.51 (dd, J = 14.1, 4.9 Hz, 1H), 3.26 (dd, J = 14.2, 10.2 Hz, 1H), 1.34 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.58, 153.36, 151.52, 147.69, 136.52, 125.29, 125.01, 83.28, 58.48, 52.32, 36.84, 27.79.

FTIR (neat) ν_{max}: 3002, 2980, 2950, 2933, 2612, 1744, 1729, 1697, 1573, 1364, 1280, 1232, 1253, 1142, and 1115 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{31}O_6N_2$, 397.19693; found, 397.19670.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (2):

1 mmol scale:

Following the general procedure, the reaction of 2-iodopyridine (207 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.9 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (344 mg, 1.36 mmol, 1.3 equiv) provided the product (371 mg, 97% yield) as a clear, colorless crystalline solid after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

25-mmol scale:

A 250-mL Schlenk flask equipped with a stir bar was charged with Hantzsch ester (6.33 g, 25 mmol, 1.0 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (22.9 mg, 0.025 mmol, 0.001 equiv), methyl-2-(di(*tert*-butoxycarbonyl)amino)but-2-enoate (9.03, 30 mmol, 1.2 equiv), 2-bromopyridine (3.95 g, 25 mmol, 1.0 equiv), and degassed DMSO/H_2O (5/1, V/V; 230 mL). The tube was connected to a N_2 line, and N_2 was streamed over the headspace of the reaction for 10 minutes before sealing with a rubber septum. The suspension was stirred under irradiation with blue LEDs for 18 hours. The reaction was quenched with saturated sodium bicarbonate solution (1200 mL) and extracted with ethyl acetate (3 x 250 mL). The extracts were combined, passed through a silica plug, and

concentrated by rotary evaporation. The residue was purified by flash column chromatography (5 – 60% ethyl acetate/hexanes) to afford the title compound (8.0 g, 84% yield) as a white crystalline solid.

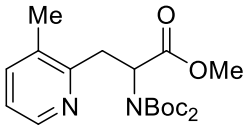
Mp: 49 – 51 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J = 4.8 Hz, 1H), 7.50 (td, J = 7.7, 1.9 Hz, 1H), 7.09 – 7.00 (m, 2H), 5.45 (dd, J = 9.3, 5.2 Hz, 1H), 3.65 (s, 3H), 3.57 (dd, J = 14.2, 5.1 Hz, 1H), 3.25 (dd, J = 14.2, 9.4 Hz, 1H), 1.34 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.82, 157.95, 151.51, 149.34, 136.17, 123.86, 121.42, 82.87, 58.16, 52.21, 38.76, 27.81.

FTIR (neat) ν_{max}: 3002, 2977, 2950, 2936, 1742, 1724, 1689, 1378, 1365, 12533, 1234, 1163, 1121, 1010, and 776 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{29}O_6N_2$, 381.20201; found, 381.20181.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(3-methylpyridin-2-yl)propanoate (3):

Following the general procedure, the reaction of 2-bromo-3-methylpyridine (175 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (604 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.9 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (344 mg, 1.36 mmol,

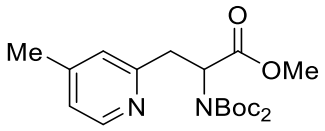
1.3 equiv) provided the product (376 mg, 94% yield) as a pale yellow oil after purification by flash column chromatography (2% – 6% tetrahydrofuran/dichloromethane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 – 8.29 (m, 1H), 7.38 – 7.28 (m, 1H), 6.97 (dd, J = 7.6, 4.8 Hz, 1H), 5.64 (dd, J = 8.9, 5.1 Hz, 1H), 3.69 (s, 3H), 3.58 (dd, J = 14.8, 5.1 Hz, 1H), 3.34 (dd, J = 14.8, 8.9 Hz, 1H), 2.27 (s, 3H), 1.38 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.11, 156.41, 151.69, 146.65, 137.44, 131.65, 121.34, 82.82, 57.94, 52.21, 35.36, 27.86, 18.72.

FTIR (neat) ν_{max}: 2979, 2952, 2935, 1793, 1743, 1698, 1575, 1451, 1436 ,1366, 1227, 1167, 1141, 1116, and 778 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{31}O_6N_2$, 395.21766; found, 395.21744.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(4-methylpyridin-2-yl)propanoate (4):

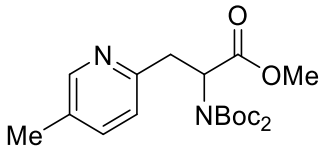
Following the general procedure, the reaction of 2-bromo-4-methylpyridine (173 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.6 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (331 mg, 1.31 mmol, 1.3 equiv) provided the product (377 mg, 96% yield) as a pale yellow oil after purification by flash column chromatography (2% – 6% tetrahydrofuran/dichloromethane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 5.8 Hz, 1H), 6.89 (s, 2H), 5.46 (dd, J = 9.3, 5.1 Hz, 1H), 3.68 (s, 3H), 3.55 (dd, J = 14.2, 5.1 Hz, 1H), 3.22 (dd, J = 14.2, 9.4 Hz, 1H), 2.24 (s, 3H), 1.37 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.90, 157.72, 151.53, 149.12, 147.15, 124.75, 122.43, 82.84, 58.21, 52.22, 38.66, 27.82, 20.88.

FTIR (neat) ν_{max}: 2978, 2952, 2935, 1794, 1740, 1606, 1366, 1270, 1251, 1227, 1166, 1138, 852, and 778 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{31}O_6N_2$, 395.21766; found, 395.21746.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-methylpyridin-2-yl)propanoate (5):

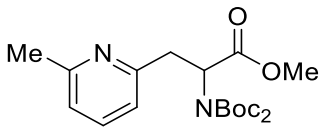
Following the general procedure, the reaction of 2-bromo-5-methylpyridine (175 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (604 mg, 2.01 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the product (373 mg, 93% yield) as a pale yellow oil after purification by flash column chromatography (3% – 8% tetrahydrofuran/dichloromethane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 – 8.24 (m, 1H), 7.45 – 7.31 (m, 1H), 6.98 (dd, J = 7.8, 0.8 Hz, 1H), 5.44 (dd, J = 9.4, 5.2 Hz, 1H), 3.69 (s, 3H), 3.56 (dd, J = 14.1, 5.2 Hz, 1H), 3.25 (dd, J = 14.1, 9.4 Hz, 1H), 2.24 (s, 3H), 1.38 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 154.92, 151.52, 149.74, 136.74, 130.69, 123.33, 82.85, 58.31, 52.21, 38.31, 27.83, 17.99.

FTIR (neat) ν_{max}: 2978, 2952, 2935, 1793, 174, 1710, 1366, 1270, 1167, 1137, and 808 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{30}O_6N_2$, 395.21766; found, 395.21729.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(6-methylpyridin-2-yl)propanoate (6):

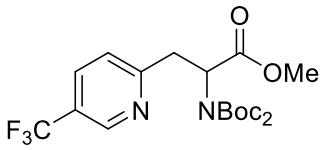
Following the general procedure, the reaction of 2-bromo-6-methylpyridine (175 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (606 mg, 2.01 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.1 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (334 mg, 1.30 mmol, 1.3 equiv) provided the product (388 mg, 97% yield) as a pale yellow oil after purification by flash column chromatography (3% – 8% tetrahydrofuran/dichloromethane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, J = 7.6 Hz, 1H), 6.90 (dd, J = 17.4, 7.6 Hz, 2H), 5.44 (dd, J = 9.7, 5.1 Hz, 1H), 3.69 (s, 3H), 3.53 (dd, J = 14.0, 5.1 Hz, 1H), 3.26 (dd, J = 13.9, 9.7 Hz, 1H), 2.46 (s, 3H), 1.37 (d, J = 0.9 Hz, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 157.86, 157.13, 136.44, 120.97, 120.85, 82.80, 58.34, 52.21, 38.69, 27.83, 24.48.

FTIR (neat) ν_{max}: 3000, 2980, 2957, 2933, 1743, 172, 1689, 1579, 1456, 1430, 1377, 1364, 1278, 1246, 1231, 1166, 1011, and 788 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{31}O_6N_2$, 395.21766; found, 395.21699.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-(trifluoromethyl)pyridin-2-yl)propan-oate (7):

Following the general procedure, the reaction of 2-bromo-5-(trifluoromethyl)pyridine (225 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (605 mg, 2.01 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.6 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided the product (420 mg, 94% yield) as a pale yellow oil after purification by flash column chromatography (3% – 12% tetrahydrofuran/hexanes).

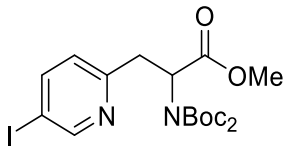
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 – 8.68 (m, 1H), 7.76 (dd, J = 8.1, 2.2 Hz, 1H), 7.28 – 7.16 (m, 1H), 5.50 (dd, J = 8.7, 5.8 Hz, 1H), 3.71 – 3.59 (m, 4H), 3.34 (dd, J = 14.3, 8.8 Hz, 1H), 1.37 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 177.59, 170.73, 151.91, 149.99, 147.13, 140.05, 128.86, 121.72, 83.33, 57.75, 52.38, 39.37, 32.46, 27.83, 27.48.

^{19}F NMR (282 MHz, $CDCl_3$) δ -62.45.

FTIR (neat) ν_{max}: 2981, 2954, 2936, 1793, 1745, 1700, 1608, 1367, 1381, 1271, 1161, 1127, 1017, and 756 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{28}O_6N_2F_3$, 449.18940; found, 449.18909.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-iodopyridin-2-yl)propanoate (8):

Following the general procedure, the reaction of 2,5-diiodopyridine (333 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (601 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.1 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (321 mg, 1.27 mmol, 1.3 equiv) provided the product (378 mg, 74% yield) as white solid after purification by flash column chromatography (0% – 30% tetrahydrofuran/hexanes).

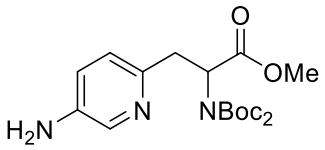
Mp: 59 – 62 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 8.66 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.81 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.41 (dd, *J* = 9.0, 5.6 Hz, 1H), 3.66 (s, 3H), 3.51 (dd, *J* = 14.2, 5.6 Hz, 1H), 3.20 (dd, *J* = 14.2, 9.0 Hz, 1H), 1.37 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.62, 156.96, 155.24, 151.58, 144.31, 125.78, 90.78, 83.08, 57.81, 52.30, 38.17, 27.86.

FTIR (neat) ν_{max}: 3005, 2980, 2968, 2945, 1746, 1728, 1697, 1363, 1273, 1163, 1128, and 760 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{28}O_6N_2I$, 507.09866; found, 507.09763.



methyl 3-(5-aminopyridin-2-yl)-2-(di(*tert*-butoxycarbonyl)amino)propanoate (9):

Following the general procedure, the reaction of 6-iodopyridin-3-amine (220 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (603 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (280 mg, 71% yield) as an off-white solid after purification by flash column chromatography (50% – 100% ethyl acetate/hexanes).

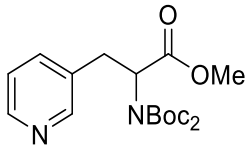
Mp: 80 – 82 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 6.82 (s, 2H), 5.33 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.72 (s, 2H), 3.66 (s, 4H), 3.44 (dd, *J* = 14.2, 5.1 Hz, 1H), 3.14 (dd, *J* = 14.2, 9.6 Hz, 1H), 1.36 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.00, 151.56, 147.17, 141.01, 136.91, 123.81, 121.93, 82.85, 58.57, 52.15, 37.70, 27.83.

FTIR (neat) ν_{max}: 3452, 3367, 2983, 2970, 2943, 1730, 1718, 1488, 1366, 1218, 1141, and 1115 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{30}O_6N_3$, 396.21291; found, 396.21126.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-3-yl)propanoate (10):

Following the general procedure, the reaction of 3-iodopyridine (205 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (609 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.2 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (279 mg, 73% yield) as a clear, colorless crystalline solid after purification by flash column chromatography (20% – 50% ethyl acetate/hexanes).

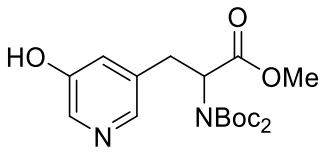
Mp: 76 – 78 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 8.4, 3.5 Hz, 2H), 7.44 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 7.8, 4.8 Hz, 1H), 5.06 (dd, J = 10.3, 5.2 Hz, 1H), 3.66 (s, 3H), 3.34 (dd, J = 14.2, 5.2 Hz, 1H), 3.15 (dd, J = 14.3, 10.3 Hz, 1H), 1.30 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (100 MHz, Chloroform-d) δ 170.36, 151.59, 150.72, 147.95, 136.93, 132.99, 123.14, 83.25, 58.69, 52.32, 33.34, 27.75.

FTIR (neat) ν_{max}: 2975, 2951, 1793, 1739, 1392, 1368, 1138, 1112 1103, and 718 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{19}H_{29}O_6N_2$, 381.20201; found, 381.20154.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-hydroxypyridin-3-yl)propanoate (11): Following the general procedure, the reaction of 5-iodopyridin-3-ol (220 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (371 mg, 1.47 mmol, 1.5 equiv) provided the product (265 mg, 67% yield) as an off-white solid oil after purification by flash column chromatography (50% – 100% ethyl acetate/hexanes).

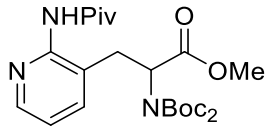
Mp: 112 – 116 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 2.6 Hz, 1H), 7.94 (d, J = 1.7 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 5.14 (dd, J = 10.2, 5.0 Hz, 1H), 3.74 (s, 3H), 3.41 (dd, J = 14.2, 5.0 Hz, 1H), 3.16 (dd, J = 14.2, 10.2 Hz, 1H), 1.38 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.36, 154.82, 151.64, 140.21, 135.31, 134.98, 125.44, 83.62, 58.83, 52.45, 33.27, 27.79.

FTIR (neat) ν_{max}: 2980, 2581, 1744, 1696, 1437, 1366, 1269, 1222, and 1166 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{29}O_7N_2$, 397.19693; found, 397.19621.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-pivalamidopyridin-3-yl)propanoate (12): Following the general procedure, the reaction of N-(3-iodopyridin-2-yl)pivalamide (302 mg, 0.99 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (609 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.9 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (380 mg, 1.50 mmol, 1.5 equiv) provided the product (347 mg, 73% yield) as a white solid after purification by flash column chromatography (20% – 100% ethyl acetate/hexanes).

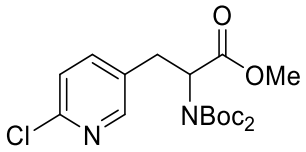
Mp: 104 – 107 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.30 (dd, J = 4.8, 1.8 Hz, 1H), 7.49 (dd, J = 7.6, 1.9 Hz, 1H), 7.05 (dd, J = 7.6, 4.8 Hz, 1H), 5.21 (dd, J = 8.5, 6.0 Hz, 1H), 3.66 (s, 3H), 3.46 (dd, J = 14.5, 6.0 Hz, 1H), 3.01 (dd, J = 14.5, 8.6 Hz, 1H), 1.34 (s, 18H), 1.29 (s, 9H).

^{13}C NMR (75MHz, $CDCl_3$) δ 177.59, 170.73, 151.91, 149.99, 147.13, 140.05, 128.86, 121.72, 83.33, 57.75, 52.38, 39.37, 32.46, 27.83, 27.48.

FTIR (neat) ν_{max}: 3160, 2970, 1749, 1738, 1697, 1437, 1365, and 1140 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{38}O_7N_3$, 480.27043; found, 480.26943.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(6-chloropyridin-3-yl)propanoate (13):

Following the general procedure, the reaction of 2-chloro-5-iodopyridine (240 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.7 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (379 mg, 1.50 mmol, 1.5 equiv) provided the product (318 mg, 77% yield) as a clear, colorless crystalline solid after purification by flash column chromatography (3% – 25% tetrahydrofuran/hexanes).

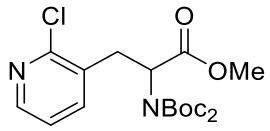
Mp: 87 – 90 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 1.9 Hz, 1H), 7.49 (dd, J = 8.2, 2.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 5.09 (dd, J = 10.0, 5.4 Hz, 1H), 3.73 (s, 3H), 3.38 (dd, J = 14.3, 5.4 Hz, 1H), 3.20 (dd, J = 14.2, 10.0 Hz, 1H), 1.39 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.21, 151.77, 150.50, 149.81, 139.90, 132.05, 123.80, 83.55, 58.48, 52.46, 32.69, 27.81.

FTIR (neat) ν_{max}: 3007, 1970, 1954, 2937, 2916, 2848, 1743, 1729, 1690, 1340, 1274, 1201, 1161, 1019, and 758 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{28}O_6N_2Cl$, 415.16438; found, 415.16376.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-chloropyridin-3-yl)propanoate (14):

Following the general procedure, the reaction of 2-chloro-3-iodopyridine (239 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (611 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.2 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (383 mg, 1.51 mmol, 1.5 equiv) provided the product (306 mg, 74% yield) as a white crystalline solid after purification by flash column chromatography (10% – 30% ethyl acetate/hexanes).

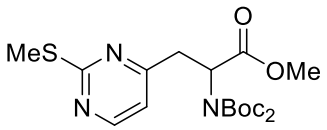
Mp: 71 – 74 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 1H), 7.45 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.12 (dd, *J* = 7.5, 4.8 Hz, 1H), 5.24 (dd, *J* = 10.8, 4.3 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.26 (dd, *J* = 14.2, 10.8 Hz, 1H), 1.33 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.20, 151.76, 151.28, 148.04, 140.43, 132.15, 122.51, 83.39, 56.99, 52.44, 33.73, 27.76.

FTIR (neat) ν_{max}: 2980, 2952, 2936, 1794, 1745, 1696, 1367, 1137, 1126, and 748 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{28}O_6N_2Cl$, 415.16304; found, 415.16225.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-(methylthio)pyrimidin-4-yl) propano-ate (15):

Following the general procedure, the reaction of 4-iodo-2-(methylthio)pyrimidine (249 mg, 0.99 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (370 mg, 1.46 mmol, 1.5 equiv) provided the product (338 mg, 80% yield) as a white crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

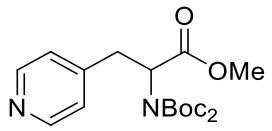
Mp: 71 – 75 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 5.0 Hz, 1H), 6.78 (d, J = 5.0 Hz, 1H), 5.46 (dd, J = 9.2, 5.4 Hz, 1H), 3.68 (s, 3H), 3.45 (dd, J = 14.2, 5.5 Hz, 1H), 3.19 (dd, J = 14.2, 9.2 Hz, 1H), 2.47 (s, 3H), 1.38 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.34, 170.44, 166.83, 156.94, 151.56, 116.27, 83.26, 57.06, 52.38, 37.99, 27.83, 13.94.

FTIR (neat) ν_{max}: 2983, 2940, 1948, 1703, 1565, 1550, 1451, 1296, 1162, 1136, and 778 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{28}O_6N_3S$, 428.18498; found, 428.18414.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-4-yl)propanoate (16):

Following the general procedure, the reaction of 4-iodopyridine (205 mg, 1.00 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (609 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.2 mg, 0.012 mmol, 0.01 equiv) and Hantzsch ester (376 mg, 1.50 mmol, 1.5 equiv) provided the product (129 mg, 34% yield) as a white crystalline solid after purification by flash column chromatography (10% – 80% ethyl acetate/hexanes).

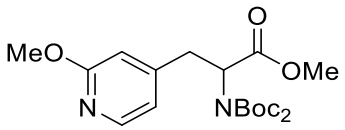
Mp: 97 – 100 °C

^{1}H NMR (500 MHz, CDCl3) δ 8.49 – 8.41 (m, 2H), 7.10 (d, J = 5.7 Hz, 2H), 5.15 (dd, J = 10.1, 5.3 Hz, 1H), 3.72 (s, 3H), 3.40 (dd, J = 14.0, 5.3 Hz, 1H), 3.19 (dd, J = 14.0, 10.2 Hz, 1H), 1.37 (s, 18H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.32, 151.69, 149.68, 146.72, 124.84, 83.35, 58.26, 52.41, 35.65, 27.80.

FTIR (neat) ν_{max}: 3005, 2970, 2948, 1748, 1736, 1690, 1366, 1228, 1217, and 1140 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{29}O_6N_2$, 381.20201; found, 381.20167.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(5-methoxypyridin-3-yl)propanoate (17):

Following the general procedure, the reaction of 4-bromo-2-methoxypyridine (195 mg, 1.04 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (604 mg, 2.01 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (385 mg, 1.52 mmol, 1.5 equiv) provided the product (280 mg, 66% yield) as a white crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

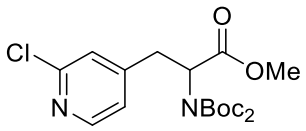
Mp: 69 – 72 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, J = 5.3, 0.7 Hz, 1H), 6.67 (dd, J = 5.3, 1.5 Hz, 1H), 6.52 (dd, J = 1.5, 0.7 Hz, 1H), 5.12 (dd, J = 10.2, 5.1 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.32 (dd, J = 13.9, 5.1 Hz, 1H), 3.12 (dd, J = 13.9, 10.2 Hz, 1H), 1.36 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.39, 164.30, 151.60, 149.37, 146.61, 118.11, 111.57, 83.24, 58.24, 53.21, 52.39, 35.48, 27.76.

FTIR (neat) ν_{max}: 2979, 2950, 1745, 1697, 1613, 1561, 1380, 1270, 1244, 1136, 1112, and 774 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{31}O_7N_2$, 411.21258; found, 411.21182.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-chloropyridin-4-yl)propanoate (18):

Following the general procedure, the reaction of 2-chloro-4-iodopyridine (244 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (390 mg, 1.54 mmol, 1.5 equiv) provided the product (352 mg, 83% yield) as a white crystalline solid after purification by flash column chromatography (10% – 30% ethyl acetate/hexanes).

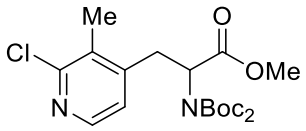
Mp: 104 – 108 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 5.1 Hz, 1H), 7.13 (s, 1H), 7.04 (dd, *J* = 5.1, 1.5 Hz, 1H), 5.12 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.71 (s, 3H), 3.38 (dd, *J* = 14.0, 5.4 Hz, 1H), 3.18 (dd, *J* = 14.0, 10.0 Hz, 1H), 1.38 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.04, 151.74, 151.47, 150.18, 149.47, 125.22, 123.61, 83.59, 57.91, 52.52, 35.34, 27.80.

FTIR (neat) ν_{max}: 3054, 3001, 2982, 2972, 1743, 1727, 1692, 1596, 1375, 1275, 1139, 1128, and 1010 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{28}O_6N_2Cl$, 415.16304; found, 415.16263.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(2-chloro-3-methylpyridin-4-yl) propanoate (19):

Following the general procedure, the reaction of 2-chloro-4-iodo-3-methylpyridine (250 mg, 0.99 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (600 mg, 1.99 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (381 mg, 1.51 mmol, 1.5 equiv) provided the product (330 mg, 78% yield) as a white crystalline solid after purification by flash column chromatography (0% – 30% tetrahydrofuran/hexanes).

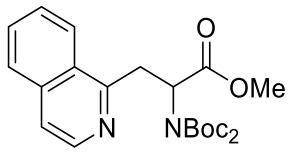
Mp: 83 – 86 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 4.9, 0.7 Hz, 1H), 6.93 (d, J = 4.9 Hz, 1H), 5.10 (dd, J = 10.7, 4.7 Hz, 1H), 3.71 (s, 3H), 3.43 (dd, J = 14.1, 4.7 Hz, 1H), 3.28 (dd, J = 14.1, 10.7 Hz, 1H), 2.33 (s, 3H), 1.33 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.07, 152.30, 151.69, 147.95, 146.12, 131.69, 124.78, 83.48, 57.40, 52.50, 33.75, 27.72, 15.62.

FTIR (neat) ν_{max}: 2996, 2980, 2955, 2936, 1752, 1741, 1706, 1365, 1249, 1136, 1113, and 1015 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{30}O_6N_2Cl$, 429.17869; found, 429.17794.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(isoquinolin-1-yl)propanoate (20):

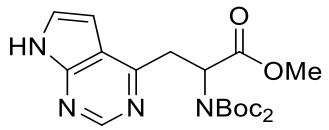
Following the general procedure, the reaction of 1-iodoisoquinoline (260 mg, 1.02 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (610 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (371 mg, 1.47 mmol, 1.5 equiv) provided the product (381 mg, 87% yield) as a colorless oil after purification by flash column chromatography (1% – 10% tetrahydrofuran/dichloromethane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 5.7 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.71 – 7.62 (m, 1H), 7.57 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.51 (d, J = 5.7 Hz, 1H), 5.77 (dd, J = 9.1, 4.7 Hz, 1H), 4.15 (dd, J = 15.1, 4.7 Hz, 1H), 3.93 (dd, J = 15.1, 9.1 Hz, 1H), 3.76 (s, 3H), 1.34 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 171.06, 158.10, 151.73, 141.96, 136.17, 129.83, 127.54, 127.28, 127.13, 124.95, 119.46, 82.85, 58.20, 52.39, 35.13, 27.80.

FTIR (neat) ν_{max}: 2978, 1793, 1741, 1696, 1366, 1381, 1273, 1251, 1226, 1135, 1109, and 764 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{31}O_6N_2$, 431.21766; found, 431.21682.



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(7H-pyrrolo[2,3-d]pyrimidin-4-yl) prop-anoate (21):

Following the general procedure, the reaction of 4-bromo-7H-pyrrolo[2,3-d]pyrimidine (199 mg, 1.01 mmol, 1 equiv), methyl 2-(di(*tert*-butoxycarbonyl)amino)acrylate (611 mg, 2.03 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.o mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (381 mg, 1.51 mmol, 1.5 equiv) provided the product (401 mg, 95% yield) as an off-white crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

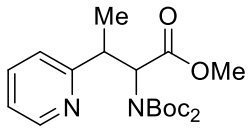
Mp: 112 – 114 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.84 (s, 1H), 8.82 (s, 1H), 7.35 (dd, J = 3.6, 2.2 Hz, 1H), 6.56 (dd, J = 3.6, 1.8 Hz, 1H), 5.72 (dd, J = 9.0, 5.1 Hz, 1H), 3.88 (dd, J = 14.4, 5.2 Hz, 1H), 3.72 (s, 3H), 3.67 (dd, J = 14.4, 9.0 Hz, 1H), 1.35 (s, 18H).

^{13}C NMR (75MHz, $CDCl_3$) δ 170.73, 159.19, 151.62, 151.44, 150.75, 125.53, 118.46, 99.57, 83.12, 57.58, 52.45, 36.01, 27.80.

FTIR (neat) ν_{max}: 3127, 3002, 2974, 2852, 1745, 1691, 1583, 1379, 1346, 1142, 1119, 971, and 748 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{29}O_6N_4$, 421.20816; found, 421.20734.



methyl 2-(di(tert-butoxycarbonyl)amino)-3-(pyridin-2-yl)butanoate (25):

Following the general procedure, the reaction of 2-bromopyridine (161 mg, 1.02 mmol, 1 equiv), methyl-2-(di(tert-butoxycarbonyl)amino)but-2-enoate (638 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.4 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided an inseparable 3:1 mixture of diastereomers (261 mg, 66% yield) as a white crystalline solid after purification by flash column chromatography (10% – 60% ethyl acetate/hexanes).

For the mixture of diastereomers:

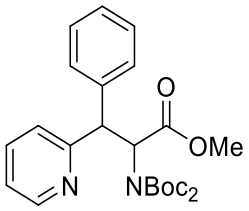
Mp: 84 – 88 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 – 8.49 (m, $1H_{dr1}$ + $1H_{dr2}$), 7.60 (td, J = 7.6, 1.9 Hz, $1H_{dr1}$), 7.55 (td, J = 7.6, 1.9 Hz, $1H_{dr2}$), 7.25 (d, J = 7.9 Hz, $1H_{dr1}$), 7.12 (d, J = 7.8 Hz, $1H_{dr2}$), 7.09 (m, $1H_{dr1}$+$1H_{dr2}$), 5.95 (d, J = 9.8 Hz, $1H_{dr1}$), 5.17 (d, J = 9.7 Hz, $1H_{dr2}$), 3.87 (dq, J = 9.7, 6.7 Hz, $1H_{dr2}$), 3.76 (m, $1H_{dr1}$ + $3H_{dr2}$), 3.58 (s, $3H_{dr1}$), 1.58 (d, J = 7.2, $1H_{dr2}$) 1.56 (s, $18H_{dr1}$), 1.42 (s, $18H_{dr2}$), 1.18 (d, J = 7.2 Hz, $3H_{dr1}$).

^{13}C NMR (150 MHz, $CDCl_3$) δ 171.05, 171.03, 164.27, 162.63, 152.39, 151.77, 149.31, 149.06, 136.19, 135.96, 123.26, 123.15, 121.37, 121.14, 83.10, 82.63, 62.12, 61.10, 52.11, 42.72, 28.02, 27.90, 20.26, 18.57

FTIR (neat) ν_{max}: 2979, 2936, 1793, 1745, 1699, 1523, 1365, 1143, 1122, 1104, 845, 758, and 749 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{31}O_6N_2$, 395.21766; found, 395.21700.



methyl 2-(di(tert-butoxycarbonyl)amino)-3-phenyl-3-(pyridin-2-yl)propanoate (26):

Following the general procedure, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1 equiv), methyl 2-(di(tert-butoxycarbonyl)amino)-3-phenylacrylate (750 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.0 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (340 mg, 1.34 mmol, 1.3 equiv) provided an inseparable 4:1 mixture of diastereomers (246 mg, 54% yield) as a colorless oil after purification by flash column chromatography (10% – 60% ethyl acetate/hexanes).

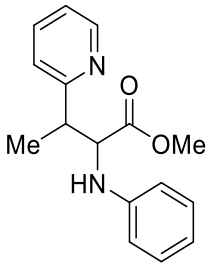
For the mixture of diastereomers:

^{1}H NMR (600 MHz, C_6D_6) δ 8.44 (ddd, J = 4.9, 1.9, 0.9 Hz, $1H_{dr1}$), 8.40 (ddd, J = 4.8, 1.9, 0.9 Hz, $1H_{dr2}$), 7.88 – 7.82 (m, $2H_{dr2}$), 7.60 (d, J = 6.9 Hz, $2H_{dr1}$), 7.27 (d, J = 10.2 Hz, $1H_{dr1}$), 7.13 (t, J = 7.7 Hz, $2H_{dr2}$), 7.10 (d, J = 7.9 Hz, $1H_{dr2}$), 7.07 (t, J = 7.7 Hz, $2H_{dr1}$), 7.01 (d, J =8.1, $1H_{dr1}$), 6.99 – 6.93 (m, $2H_{dr1}$ + $2H_{dr2}$), 6.54 (ddd, J = 7.3, 4.9, 1.3 Hz, $1H_{dr1}$), 6.50 (ddd, J = 7.5, 4.8, 1.2 Hz, $1H_{dr2}$), 6.42 (d, J = 10.2 Hz, $1H_{dr2}$), 5.46 (d, J = 10.3 Hz, $1H_{dr2}$), 5.35 (d, J = 10.2 Hz, $1H_{dr1}$), 3.19 (s, $3H_{dr1}$), 3.17 (s, $3H_{dr2}$), 1.38 (s, $18H_{dr2}$), 1.34 (s, $18H_{dr1}$).

^{13}C NMR (150 MHz, C_6D_6) δ 170.44, 170.10, 161.90, 161.21, 152.46, 152.18, 149.07, 148.50, 142.30, 140.57, 135.87, 135.56, 129.37, 129.05, 128.27, 128.05, 126.63, 126.58, 124.28, 123.71, 120.92, 120.87, 81.77, 81.76, 61.79, 60.10, 54.88, 53.70, 51.22, 27.67, 27.65.

FTIR (neat) ν_{max}: 2970, 2941, 1753, 1736, 1719, 1367, 1227, 1139, 1108, 770, and 755 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{25}H_{33}O_6N_2$, 457.23331; found, 457.23254.



methyl 2-(phenylamino)-3-(pyridin-2-yl)butanoate (27):

Following the general procedure, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1.0 equiv), methyl 2-(phenylamino)but-2-enoate (380 mg, 2.00 mmol, 2.0 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (10.0 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (325 mg, 1.28 mmol, 1.30 equiv) provided an inseparable 5:4 mixture of diastereomers (186 mg, 69% yield) as a yellow crystalline solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

For the mixture of diastereomers:

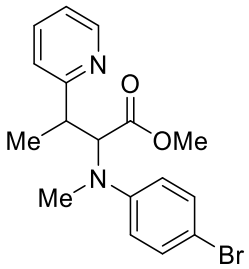
Mp: 62 – 64 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 – 8.54 (m, $1H_{dr1}$ + $1H_{dr2}$), 7.65 – 7.52 (m, $1H_{dr1}$ + $1H_{dr2}$), 7.23 – 7.07 (m, $4H_{dr1}$ + $4H_{dr2}$), 6.70 (m, $1H_{dr1}$ + $1H_{dr2}$), 6.63 (d, J = 7.6 Hz, $2H_{dr1}$), 6.58 – 6.51 (d, J = 8.0 Hz, $2H_{dr2}$), 4.97 (d, J = 8.9 Hz, $1H_{dr1}$), 4.61 (d, J = 8.3 Hz, $1H_{dr2}$), 4.42 (m, $1H_{dr1}$ + $1H_{dr2}$), 3.62 (s, $3H_{dr1}$), 3.59 (s, $3H_{dr2}$), 3.53 – 3.40 (m, $1H_{dr1}$ + $1H_{dr2}$), 1.49 (d, J = 7.1 Hz, $3H_{dr2}$), 1.44 (d, J = 7.0 Hz, $3H_{dr1}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.88, 173.55, 161.79, 161.66, 149.25, 149.16, 147.22, 147.19, 136.56, 136.51, 129.20, 129.18, 122.47, 122.38, 121.96, 118.29, 117.88, 113.68, 113.24, 61.90, 61.74, 51.94, 51.86, 44.35, 43.78, 17.45, 15.43.

FTIR (neat) ν_{max}: 3373, 3053, 2969, 2950, 1732, 1601, 1590, 1507, 1149, 908, and 691 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{19}O_2N_2$, 271.14410; found, 271.14386.



methyl 2-((4-bromophenyl)(methyl)amino)-3-(pyridin-2-yl)butanoate (28):

Following the general procedure, the reaction of 2-bromopyridine (160 mg, 1.01 mmol, 1 equiv), methyl 2-((4-bromophenyl)(methyl)amino)but-2-enoate (570 mg, 2.01 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.1 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (325 mg, 1.28 mmol, 1.3 equiv) provided an inseparable 4:3 mixture of diastereomers (311 mg, 86% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

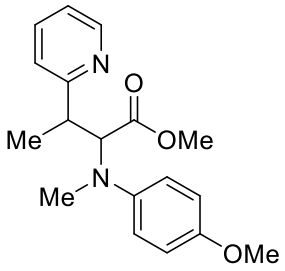
For the mixture of diastereomers:

^{1}H NMR (500 MHz, $CDCl_3$) 8.56 – 8.52 (m, $1H_{dr1}$), 8.44 (m, $1H_{dr2}$), 7.60 (td, *J* = 7.7, 1.8 Hz, $1H_{dr1}$), 7.49 (td, *J* = 7.6, 1.8 Hz, $1H_{dr2}$), 7.40 – 7.29 (m, $2H_{dr1}$), 7.23 (d, *J* = 7.8 Hz, $1H_{dr1}$), 7.18 (d, *J* = 9.0 Hz, $2H_{dr2}$), 7.12 (ddd, *J* = 7.5, 4.9, 1.2 Hz, $1H_{dr1}$), 7.06 (d, *J* = 7.8 Hz, $1H_{dr2}$), 7.03 (ddd, *J* = 7.5, 4.8, 1.2 Hz, $1H_{dr2}$), 6.85 (d, *J* = 9.1 Hz, $2H_{dr1}$), 6.59 (d, *J* = 9.0 Hz, $2H_{dr2}$), 4.98 (d, *J* = 10.8 Hz, $1H_{dr1}$), 4.78 (d, *J* = 11.0 Hz, $1H_{dr2}$), 3.72 (s, $3H_{dr2}$), 3.67 – 3.57 (m, $1H_{dr1}$ + $1H_{dr2}$), 3.46 (s, $3H_{dr1}$), 2.93 (s, $3H_{dr1}$), 2.72 (s, $3H_{dr2}$), 1.32 (d, *J* = 6.7 Hz, $3H_{dr2}$), 1.21 (d, *J* = 7.0 Hz, $3H_{dr1}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.45, 171.43, 162.71, 161.95, 149.34, 149.20, 148.88, 136.43, 136.24, 131.82, 131.41, 123.42, 122.47, 121.71, 121.62, 115.45, 115.08, 109.65, 109.54, 66.70, 65.52, 51.72, 51.52, 41.75, 41.69, 33.12, 32.78, 18.50, 18.23.

FTIR (neat) ν_{max}: 2990, 2948, 2904, 2817, 1718, 1648, 1490, 1434, 1252, 1202, 1120, 1108, 1042, 811, 776, and 766 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{20}O_2N_2Br$, 363.07027; found, 363.07074.



methyl 2-((4-methoxyphenyl)(methyl)amino)-3-(pyridin-2-yl)butanoate 29):

Following the general procedure, the reaction of 2-bromopyridine (159 mg, 1.00 mmol, 1 equiv), methyl 2-((4-methoxyphenyl)(methyl)amino)but-2-enoate (477 mg, 2.03 mmol, 2 equiv),

$[Ir(ppy)_2(dtbbpy)]PF_6$ (10.1 mg, 0.011 mmol, 0.01 equiv) and Hantzsch ester (335 mg, 1.32 mmol, 1.3 equiv) provided an inseparable 3:1 mixture of diastereomers (182mg, 58% yield) as a colorless oil after purification by flash column chromatography (5% – 40% ethyl acetate/hexanes).

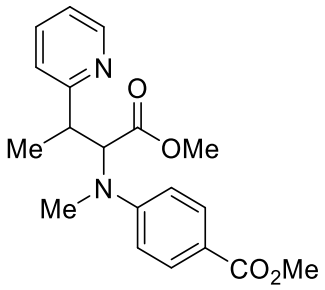
For the mixture of diastereomers:

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (ddd, J = 4.9, 1.9, 0.9 Hz, $1H_{dr2}$), 8.49 (ddd, J = 4.9, 1.9, 0.9 Hz, $1H_{dr1}$), 7.59 (td, J = 7.7, 1.9 Hz, $1H_{dr2}$), 7.50 (td, J = 7.6, 1.8 Hz, $1H_{dr1}$), 7.22 (dt, J = 7.8, 1.1 Hz, $1H_{dr2}$), 7.13 – 7.07 (m, $1H_{dr1}$ + $1H_{dr2}$), 7.04 (ddd, J = 7.6, 4.8, 1.1 Hz, $1H_{dr1}$), 6.98 – 6.92 (m, $2H_{dr2}$), 6.87 – 6.83 (m, $2H_{dr2}$), 6.75 – 6.65 (m, $4H_{dr1}$), 4.85 (d, J = 11.0 Hz, $1H_{dr2}$), 4.68 (d, J = 11.1 Hz, $1H_{dr1}$), 3.77 (s, $3H_{dr2}$), 3.64 – 3.55 (m, $1H_{dr1}$ + $1H_{dr2}$), 3.43 (s, $3H_{dr2}$), 2.91 (s, $3H_{dr2}$), 2.71 (s, $3H_{dr1}$), 1.31 (d, J = 6.7 Hz, $3H_{dr1}$), 1.27 (d, J = 7.0 Hz, $3H_{dr2}$).

^{13}C NMR (150 MHz, $CDCl_3$) δ 174.25, 174.10, 171.73, 163.11, 162.52, 152.44, 152.29, 149.28, 149.18, 144.91, 144.67, 136.36, 136.15, 123.41, 122.66, 121.57, 121.51, 116.27, 115.58, 114.61, 114.18, 83.36, 82.77, 68.54, 67.00, 55.69, 55.57, 52.99, 52.82, 51.43, 51.24, 41.69, 41.61, 33.34, 33.15, 25.78, 25.65, 18.49, 18.30, 8.04, 7.86.

FTIR (neat) ν_{max}: 3043, 2949, 2832, 1730, 1589, 1509, 1242, 1165, 1034, 991, 817, 786, and 749 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{23}O_3N_2$, 315.17032; found, 315.17028.



methyl 4-((1-methoxy-1-oxo-3-(pyridin-2-yl)butan-2-yl)(methyl)amino)benz-

oate (30):

Following the general procedure, the reaction of 2-bromopyridine (158mg, 1.00 mmol, 1 equiv), methyl 4-((1-methoxy-1-oxobut-2-en-2-yl)(methyl)amino)benzoate (530 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.1 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (340 mg, 1.34 mmol, 1.3 equiv) provided an inseparable 5:2 mixture of diastereomers (267 mg, 78% yield) as a low-melting white solid after purification by flash column chromatography (5% – 50% ethyl acetate/hexanes).

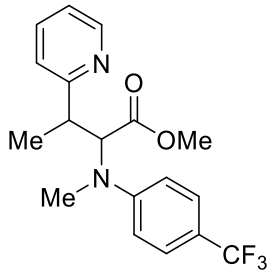
For the mixture of diastereomers:

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (ddd, J = 4.9, 1.8, 0.9 Hz, $1H_{dr1}$), 8.40 (ddd, J = 4.9, 1.8, 0.9 Hz, $1H_{dr2}$), 7.99 – 7.91 (m, $2H_{dr1}$), 7.82 – 7.77 (m, $1H_{dr2}$), 7.62 (td, J = 7.6, 1.8 Hz, $1H_{dr1}$), 7.47 (td, J = 7.7, 1.8 Hz, $1H_{dr2}$), 7.25 (d, J = 7.5 Hz, $1H_{dr1}$), 7.14 (ddd, J = 7.6, 4.8, 1.1 Hz, $1H_{dr1}$), 7.05 (dd, J = 7.7, 1.1 Hz, $1H_{dr1}$), 7.00 (ddd, J = 7.6, 4.8, 1.1 Hz, $1H_{dr2}$), 6.96 (d, J = 9.0 Hz, $2H_{dr1}$), 6.69 (d, J = 9.0 Hz, $2H_{dr2}$), 5.20 (d, J = 10.7 Hz, $1H_{dr1}$), 4.96 (d, J = 10.9 Hz, $1H_{dr2}$), 3.87 (s, $3H_{dr1}$), 3.83 (s, $3H_{dr2}$), 3.75 (s, $3H_{dr2}$), 3.71 – 3.61 (m, $1H_{dr1}$ + $1H_{dr2}$), 3.49 (s, $3H_{dr1}$), 3.04 (s, $3H_{dr1}$), 2.83 (s, $3H_{dr2}$), 1.36 (d, J = 6.7 Hz, $3H_{dr2}$), 1.19 (s, $3H_{dr1}$).

^{13}C NMR (150 MHz, $CDCl_3$) δ 171.33, 171.29, 167.22, 162.51, 161.58, 153.42, 152.98, 149.37, 149.23, 136.51, 136.30, 131.36, 130.90, 123.42, 122.32, 121.80, 121.72, 118.59, 118.40, 112.04, 111.93, 65.62, 64.74, 51.95, 51.73, 51.56, 51.50, 41.95, 41.75, 33.27, 32.92, 18.52, 18.19.

FTIR (neat) ν_{max}: 2949, 2839, 1735, 1705, 1602, 1518, 1433, 1276, 1186, 1110, and 747 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{23}O_4N_2$, 343.16523; found, 343.16512.



methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)-3-(pyridin-2-yl)butanoate (31):

Following the general procedure, the reaction of 2-bromopyridine (158 mg, 1.00 mmol, 1 equiv), methyl 2-(methyl(4-(trifluoromethyl)phenyl)amino)but-2-enoate (551 mg, 2.02 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (329 mg, 1.30 mmol, 1.3 equiv) provided an inseparable 5:2 mixture of diastereomers (274 mg, 78% yield) as a colorless oil after purification by flash column chromatography (0% – 25% ethyl acetate/hexanes).

For the mixture of diastereomers:

^{1}H NMR (600 MHz, $CDCl_3$) 8.55 (dd, *J* = 5.0, 1.7 Hz, $1H_{dr1}$), 8.41 (dd, *J* = 4.9, 1.7 Hz, $1H_{dr2}$), 7.62 (td, *J* = 7.6, 1.8 Hz, $1H_{dr1}$), 7.50 (d, *J* = 8.6 Hz, $2H_{dr1}$ + $1H_{dr2}$), 7.34 (d, *J* = 8.6 Hz, $2H_{dr2}$), 7.27 – 7.22 (m, $1H_{dr1}$), 7.16 – 7.12 (m, $1H_{dr2}$), 7.01 (m, $2H_{dr1}$ + $1H_{dr2}$), 6.74 (d, *J* = 8.6 Hz, $2H_{dr2}$),

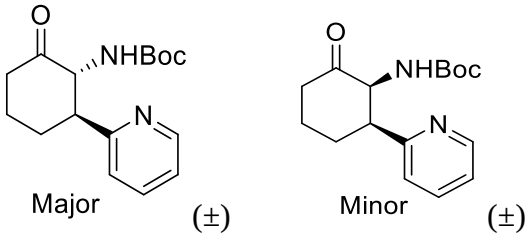
5.15 (d, J = 10.8 Hz, $1H_{dr1}$), 4.92 (d, J = 11.0 Hz, $1H_{dr2}$), 3.75 (s, $3H_{dr2}$), 3.64 (dq, J = 10.5, 7.2 Hz, $1H_{dr1}$ + $1H_{dr2}$), 3.49 (s, $3H_{dr1}$), 3.02 (s, $3H_{dr1}$), 2.80 (s, $3H_{dr2}$), 1.35 (d, J = 6.7 Hz, $3H_{dr2}$), 1.20 (d, J = 7.0 Hz, $3H_{dr1}$).

^{13}C NMR (150 MHz, $CDCl_3$) δ 171.38, 171.35, 162.54, 161.69, 152.30, 151.92, 149.37, 136.54, 136.35, 126.51 (q, J = 3.7 Hz), 126.05 (q, J = 3.7 Hz), 124.96 (q, J = 268.6), 124.92 (q, J = 268.7), 123.46, 122.41, 121.82, 118.97 (q, J = 32), 118.86 (q, J = 33), 112.59, 112.35, 65.90, 64.90, 51.91, 51.71, 41.89, 33.20, 32.83, 18.54, 18.21.

^{19}F NMR (282 MHz, CDCl3) δ -61.01.

FTIR (neat) ν_{max}: 2971, 2953, 2830, 1735, 1614, 1526, 1454, 1326, 1296, 1163, 1104, 1069, and 819 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{20}O_2N_2F_3$, 353.14714; found, 353.14797.



tert-butyl (2-oxo-6-(pyridin-2-yl)cyclohexyl)carbamate (32): Following the general procedure, 2-bromopyridine (160 mg, 1.01 mmol, 1 equiv) was reacted with tert-butyl (6-oxocyclohex-1-en-1-yl)carbamate (421 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.0 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (331 mg, 1.31 mmol, 1.3 equiv). Analysis of the crude ^{1}H NMR spectrum indicated a mixture of stereoisomers (cis:trans = 2:9), and purification by flash column

chromatography (5% – 100% ethyl acetate/hexanes) provided the title compounds (trans, 170 mg, 59% yield; cis, 52 mg, 18% yield).

Major isomer (trans):

R_f: 0.3 (50% ethyl acetate/hexanes)

Mp: 181 – 185 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 – 8.31 (m, 1H), 7.59 (td, J = 7.7, 1.8 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.12 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 5.00 (s, 1H), 4.69 – 4.51 (m, 1H), 2.97 – 2.83 (m, 1H), 2.63 – 2.43 (m, 2H), 2.32 – 1.89 (m, 3H), 1.74 (dddd, J = 16.9, 9.9, 8.6, 4.1 Hz, 1H), 1.21 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.18, 160.21, 155.18, 149.26, 136.35, 122.36, 121.98, 79.31, 62.50, 54.66, 41.08, 31.54, 28.04, 26.15.

FTIR (neat) ν_{max}: 3206, 3025, 2978, 2935, 2864, 1737, 1714, 1686, 1555, 1014, and 735 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{116}H_{23}O_3N_2$, 291.17032; found, 291.16985.

Minor isomer (cis):

R_f: 0.7 (50% ethyl acetate/hexanes)

Mp: 92 – 95 °C

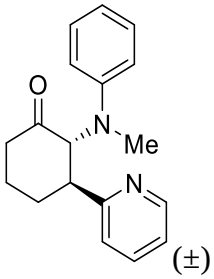
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 – 8.22 (m, 1H), 7.58 (td, J = 7.7, 1.9 Hz, 1H), 7.09 (dtd, J = 7.5, 5.2, 1.1 Hz, 2H), 5.48 (d, J = 7.3 Hz, 1H), 4.44 (ddd, J = 7.2, 5.7, 1.2 Hz, 1H), 3.98 (dt, J =

5.9, 3.9 Hz, 1H), 2.74 – 2.50 (m, 1H), 2.46 – 2.12 (m, 2H), 2.09 – 1.88 (m, 1H), 1.73 (dq, *J* = 11.2, 3.3 Hz, 2H), 1.34 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.09, 160.80, 155.71, 148.28, 136.57, 123.33, 121.51, 79.39, 60.08, 48.74, 40.26, 30.79, 28.25, 20.85.

FTIR (neat) ν_{max}: 3448, 3005, 2969, 2944, 1737, 1719, 1694, 1494, 1365, 1352, 1229, and 770 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{23}O_3N_2$, 291.17032; found, 291.16984.



(±)

2-(methyl(phenyl)amino)-3-(pyridin-2-yl)cyclohexan-1-one (33): Following the general procedure, the reaction of 2-bromopyridine (160 mg, 1.01 mmol, 1 equiv), 2-(methyl(phenyl)amino)cyclohex-2-en-1-one (401 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.5 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (330 mg, 1.30 mmol, 1.3 equiv) provided the product (196 mg, 70% yield) as a white solid after purification by flash column chromatography (10% – 80% ethyl acetate/hexanes).

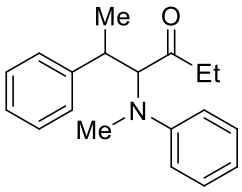
Mp: 111 – 115 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 – 8.37 (m, 1H), 7.48 (tdd, J = 7.7, 1.9, 1.0 Hz, 1H), 7.13 – 6.90 (m, 4H), 6.59 (td, J = 7.3, 1.0 Hz, 1H), 6.57 – 6.53 (m, 2H), 4.97 (d, J = 11.6 Hz, 1H), 3.60 – 3.27 (m, 1H), 2.77 (d, J = 1.0 Hz, 3H), 2.63 – 2.47 (m, 2H), 2.26 – 2.09 (m, 3H), 1.86 – 1.72 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.49, 149.02, 144.65, 143.16, 128.88, 118.43, 114.79, 39.50, 39.39, 26.01, 22.95.

FTIR (neat) ν_{max}: 2950, 2933, 2866, 1710, 1596, 1505, 745, and 690 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{21}ON_2$, 281.16484; found, 281.16465.



4-(methyl(phenyl)amino)-5-(pyridin-2-yl)hexan-3-one (34):

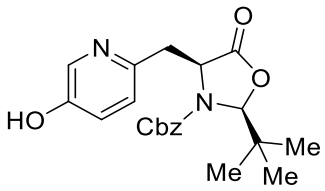
Following the general procedure, the reaction of 2-bromopyridine (159 mg, 1.00 mmol, 1 equiv), 4-(methyl(phenyl)amino)hex-4-en-3-one (406 mg, 2.00 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (9.2 mg, 0.010 mmol, 0.01 equiv) and Hantzsch ester (325 mg, 1.28 mmol, 1.3 equiv) provided the product (180 mg, 64% yield) as a yellow oil after purification by flash column chromatography (0% – 30% ethyl acetate/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.57 (td, *J* = 7.8, 1.8 Hz, 1H), 7.36 – 7.26 (m, 2H), 7.24 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.06 (ddd, *J* = 7.6, 4.9, 1.3 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.84 – 6.70 (m, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 3.62 (dq, *J* = 10.6, 7.1 Hz, 1H), 2.81 (s, 3H), 2.37 (dq, *J* = 17.7, 7.3 Hz, 1H), 2.21 (dq, *J* = 17.7, 7.3 Hz, 1H), 1.14 (d, *J* = 7.1 Hz, 3H), 0.96 – 0.70 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *δ* 208.42, 163.84, 149.80, 136.35, 129.41, 123.79, 121.22, 117.36, 112.76, 68.84, 39.67, 34.46, 32.65, 18.53, 7.42.

FTIR (neat) ν_{max}: 3061, 3027, 2976, 2937, 2906, 2816, 1682, 1625, 1597, 1499, 1355, 1339, 1310, 1221, 1184, 1164, 1109, 747, and 692 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{23}ON_2$, 283.18049; found, 283.18040.



benzyl (2S,4S)-2-(tert-butyl)-4-((5-hydroxypyridin-2-yl)methyl)-5-oxooxazolidine-3-carboxylate (33):

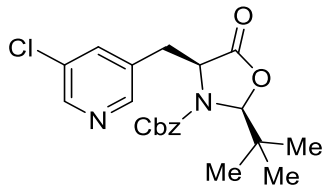
Following the general procedure, the reaction of 6-bromopyridin-3-ol (43 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (55 mg, 57% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.36 – 7.27 (m, 3H), 7.24 – 7.20 (m, 2H), 7.12 (q, J = 8.5 Hz, 2H), 5.57 (s, 1H), 5.06 (d, J = 12.0 Hz, 1H), 4.91 (t, J = 12.0 Hz, 1H), 4.75 (t, J = 6.9 Hz, 1H), 3.32 (ddd, J = 56.7, 14.1, 7.1 Hz, 2H), 1.02 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 156.0, 153.2, 146.9, 136.0, 135.2, 128.7, 128.7, 128.5, 125.5, 125.3, 96.6, 68.5, 58.0, 39.5, 37.2, 25.1.

FTIR (neat) νmax: 3066, 3033, 2960, 2925, 2872, 1790, 1717, 1575, 1481, 1392, 1346, 1335, 1272, 1228, 1198, 1172, 1121, 1037, 976, 908, 839, 720, and 668 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{23}H_{25}O_5N_2$, 385.1758; found, 385.17753.



benzyl (2S,4S)-2-(tert-butyl)-4-((2-chloropyridin-4-yl)methyl)-5-oxooxazolidine-3-carboxylate (34):

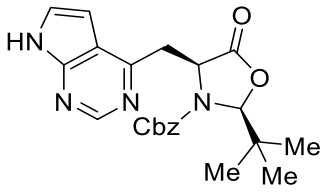
Following the general procedure, the reaction of 2-chloro-4-iodopyridine (60 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (75 mg, 75% yield) as a colorless oil after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 5.0 Hz, 1H), 7.41 – 7.38 (m, 3H), 7.27 (dd, J = 6.6, 2.8 Hz, 2H), 7.20 (s, 1H), 7.08 – 7.02 (m, 1H), 5.58 (s, 1H), 5.07 (dd, J = 70.4, 11.7 Hz, 2H), 4.43 (dd, J = 7.6, 5.4 Hz, 1H), 3.19 – 3.02 (m, 2H), 1.00 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 155.7, 151.8, 149.7, 149.1, 134.8, 129.1, 129.0, 128.8, 125.1, 123.5, 96.6, 68.9, 58.1, 38.4, 37.3, 25.0.

FTIR (neat) νmax: 3063, 3033, 2970, 2873, 1790, 1720, 1594, 1549, 1481, 1388, 1341, 1305, 1230, 1200, 1173, 1122, 1087, 1036, 980, 899, 878, 839, 746, and 698 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{21}H_{24}O_4N_2Cl$, 403.1419; found, 403.1414.



benzyl (2S,4S)-4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)methyl)-2-(tert-butyl)-5- oxooxazolidine-3-carboxylate (35):

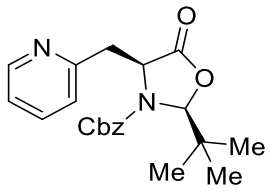
Following the general procedure, the reaction of 4-bromo-5H-pyrrolo[3,2-d]pyrimidine (50 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (82 mg, 80% yield) as a pale yellow oil after purification by flash column chromatography (20% – 70% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.78 (s, 1H), 7.31 (dd, J = 3.4, 2.3 Hz, 1H), 7.25 (d, J = 2.9 Hz, 3H), 7.12 (s, 2H), 6.57 (s, 1H), 5.63 (s, 1H), 5.19 (t, J = 6.8 Hz, 1H), 5.02 (d, J = 12.1 Hz, 1H), 4.76 (d, J = 11.0 Hz, 1H), 3.70 – 3.51 (m, 2H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 157.8, 155.8, 151.5, 150.9, 135.0, 128.6, 128.5, 128.3, 125.5, 117.9, 99.5, 96.7, 68.2, 56.7, 39.0, 37.3, 25.1.

FTIR (neat) νmax: 3202, 3133, 2969, 1792, 1721, 1585, 1393, 1349, 1307, 1230, 1194, 1119, 1043, 976, 903, 733, and 698cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{22}H_{25}O_4N_4$, 409.1870; found, 409.1866.



benzyl (2S,4S)-2-(tert-butyl)-5-oxo-4-(pyridin-2-ylmethyl)oxazolidine-3-carboxylate (36):

Following the general procedure, the reaction of 2-bromopyridine (39 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (63 mg, 68% yield) as a colorless oil after purification by flash column chromatography (10% – 40% ethyl acetate/hexanes).

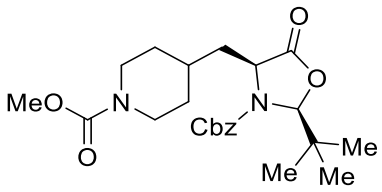
^{1}H NMR (500 MHz, CDCl3) δ 8.49 (d, J = 4.2 Hz, 1H), 7.53 (td, J = 7.7, 1.8 Hz, 1H), 7.32 (td, J = 4.8, 1.8 Hz, 3H), 7.24 (dd, J = 6.9, 2.6 Hz, 2H), 7.16 (d, J = 7.7 Hz, 1H), 7.08 (dd, J = 7.1, 5.3

Hz, 1H), 5.59 (s, 1H), 5.08 (d, J = 12.2 Hz, 1H), 4.97 (t, J = 6.9 Hz, 1H), 4.85 (d, J = 11.9 Hz, 1H), 3.38 (dd, J = 14.0, 6.9 Hz, 1H), 3.30 (dd, J = 14.0, 6.9 Hz, 1H) 1.03 (s, 9H).

^{13}C NMR (125 MHz, CDCl3) δ 172.0, 156.7, 155.9, 149.4, 136.2, 135.3, 128.6, 128.4, 128.3, 123.7, 121.9, 96.4, 68.1, 57.5, 41.4, 37.2, 25.0.

FTIR (neat) νmax: 3064, 3034, 3010, 2970, 2873, 1791, 1716, 1593, 1475, 1438, 1391, 1347, 1305, 1231, 1173, 1190, 1121, 1036, 977, 932, 825, 731, and 697 cm^{-1} .

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{21}H_{25}O_4N_2$, 369.1809; found, 369.1804.



benzyl (2S,4S)-2-(tert-butyl)-4-((1-(methoxycarbonyl)piperidin-4-yl)methyl)-5-oxooxazolidine-3-carboxylate (38):

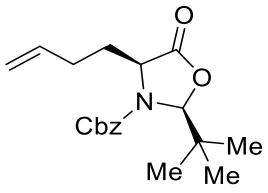
Following the general procedure, the reaction of 4-(1,3-dioxoisoindolin-2-yl) 1-methyl piperidine-1,4-dicarboxylate (83 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.5 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (93 mg, 86% yield) as a white solid after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 5H), 5.59 – 5.39 (m, 3H), 4.66 (d, J = 11.0 Hz, 1H), 4.06 – 3.52 (m, 7H), 2.52 – 2.20 (m, 2H), 1.82 (dd, J = 14.1, 7.6 Hz, 1H), 1.65 – 1.35 (m, 3H), 1.06 (s, 9H), 0.93 – 0.66 (m, 1H).

13C NMR (125 MHz, $CDCl_3$) δ 168.5, 156.0, 153.9, 134.6, 129.7, 129.1, 128.8, 95.6, 71.7, 68.1, 52.5, 44.1, 43.6, 38.8, 37.1, 31.5, 26.9.

FTIR (neat) νmax: 2959, 2852, 1792, 1724, 1701, 1472, 1448, 1396, 1309, 1258, 1193, 1125, 1043, 966, 916, 757, 731, and 699 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for C23H33O6N2, 433.2333; found, 433.2333.



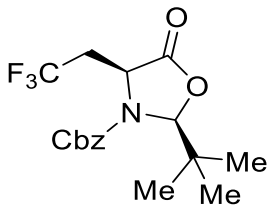
benzyl (2S,4S)-4-(but-3-en-1-yl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (39): Following the general procedure, the reaction of 3-bromoprop-1-ene (22 µL, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (35 mg, 42% yield) as a colorless oil after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 5H), 5.76 (td, J = 16.7, 6.7 Hz, 1H), 5.55 (s, 1H), 5.22 – 5.12 (td J = 16.9, 11.9 Hz , 2H), 5.06 (d, J = 17.1 Hz, 1H), 4.98 (d, J = 11.2 Hz, 1H), 4.30 (dd, J = 7.8, 6.7 Hz, 1H), 2.34 (m, 2H), 2.06 – 1.98 (m, 1H), 1.90 (m, 1H), 0.96 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 156.1, 137.0, 135.3, 128.8, 128.8, 128.6, 115.9, 96.4, 68.5, 56.5, 37.1, 32.5, 30.3, 25.0.

FTIR (neat) νmax: 3068, 3034, 2960, 2873, 1790, 1716, 1641, 1391, 1324, 1282, 1195, 1117, 1041, 979, 914, and 968 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{19}H_{26}O_4N$, 332.1856; found, 332.1859.



benzyl (2S,4S)-2-(tert-butyl)-5-oxo-4-(2,2,2-trifluoroethyl)oxazolidine-3-carboxylate (40):

A 20-mL screw-top test tube equipped with a stir bar was charged with **32** (289 mg, 1.0 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mg, 0.005 mmol, 0.01 equiv) and Hantzsch ester (164 mg, 0.65 mmol. 1.3 equiv). The tube was sealed PTFE/silicon septum and connected to a Schlenk line. The atmosphere was exchanged by applying vacuum and backfilling with N_2 (this process was conducted a total of three times). The reaction vial was disconnected from the nitrogen line and massed. The trifluoromethyl iodide lecture bottle outlet was fitted with a rubber septum, and a cannula needle (cooled to -78 °C) was used to condense trifluoromethyl iodide into the reaction tube. The reaction tube and contents were massed once more to measure the loading of

trifluoromethyl iodide (861 mg, 4.4 mmol, 4.4 equiv). The reaction was then stirred for 18 hours under irradiation by blue LEDs. The reaction was quenched with aqueous sodium bicarbonate then extracted with ethyl acetate (5 x 25 mL). The combined extracts were dried over sodium sulfate then concentrated by rotary evaporation to provide the product (222 mg, 93% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

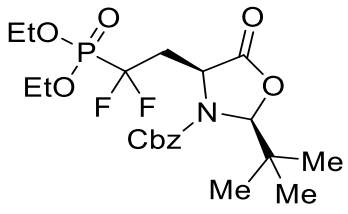
^{1}H NMR (500 MHz, DMSO-d6, 80 °C) δ 7.44 – 7.34 (m, 7H), 5.43 – 5.34 (m, 2H), 4.92 (s, 1H), 3.58 (s, 1H), 3.43 (dq, J = 15.5, 10.2 Hz, 1H), 3.17 (s, 1H), 0.94 (s, 9H).

^{13}C NMR (126 MHz, DMSO-d6, 80 °C) δ 165.3, 152.5, 133.8, 128.4, 128.3, 128.1, 124.3 (q, J = 278.6 Hz), 95.9, 68.0, 66.7, 37.6, 33.8 (q, J = 28.5), 26.0.

^{19}F NMR (282 MHz, $CDCl_3$) δ -59.92.

FTIR (neat) νmax: 3035, 2965, 1799, 1732, 1483, 1394, 1333, 1290, 1230, 1200, 1138, 1117, 1044, 1018, 976, 916, 819, 798, 767, 755, and 696 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{17}H_{21}O_4NF_3$, 360.1417; found, 360.1421.



benzyl (2S,4S)-2-(tert-butyl)-4-(2-(diethoxyphosphoryl)-2,2-difluoroethyl)-5- oxooxazol-idine-3-carboxylate (41):

Following the general procedure, the reaction of 2-bromo-2,2-diethyl (bromodifluoromethyl)phosphonate (89 µL, 0.5 mmol, 1 equiv), **32** (289 mg, 1.0 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mg, 0.005 mmol, 0.01 equiv) and Hantzsch ester (164 mg, 0.65 mmol, 1.3 equiv) provided the product (222 mg, 93% yield) as a colorless oil after purification by flash column chromatography (10% – 50% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 5H), 5.59 (s, 1H), 5.24 – 5.11 (m, 2H), 4.84 (t, J = 5.9 Hz, 1H), 4.24 (tddd, J = 12.4, 6.8, 5.2, 2.7 Hz, 4H), 2.77 – 2.48 (m, 2H), 1.35 (td, J = 7.0, 1.0 Hz, 6H), 0.95 (s, 9H).

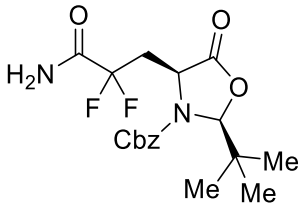
^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 155.6, 135.1, 128.6, 128.5, 121.0, 119.6, 119.3, 117.9, 117.6, 116.1, 96.8, 68.5, 64.9, 64.8, 64.8, 64.8, 51.1, 51.1, 51.0, 51.0, 37.3, 37.1, 37.0, 36.9, 24.8, 16.4, 16.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -113.20 (dddd, J = 299.8, 103.3, 32.6, 7.5 Hz).

^{31}P NMR (243 MHz, $CDCl_3$) δ 5.81 (tt, J = 104.4, 7.6 Hz).

FTIR (neat) νmax: 2976, 2875, 1796, 1720, 1482, 1392, 1291, 1270, 1236, 1197, 1177, 1105, 1010, 977, 791, 732, and 698 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{21}H_{31}O_7NF_2P$, 478.1801; found, 478.1802.



benzyl (2S,4S)-4-(3-amino-2,2-difluoro-3-oxopropyl)-2-(tert-butyl)-5-oxooxazolidine3-carboxylate (42): Following the general procedure, the reaction of 2-bromo-2,2-difluoroacetamide (43 mg, 0.25 mmol, 1 equiv), **32** (145 mg, 0.50 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mg, 0.0025 mmol, 0.01 equiv) and Hantzsch ester (82 mg, 0.33 mmol, 1.3 equiv) provided the product (58 mg, 60% yield) as a colorless oil after purification by flash column chromatography (5% – 30% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 6.40 (s, 1H), 6.13 (s, 1H), 5.58 (s, 1H), 5.26 – 5.08 (m, 2H), 4.70 (dd, J = 7.5, 5.9 Hz, 1H), 2.82 – 2.60 (m, 2H), 0.96 (s, 9H).

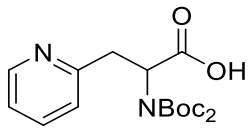
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 165.4 (t, J = 29.0 Hz), 155.9, 135.1, 128.8, 128.8, 128.7, 116.0 (t, J = 254.8 Hz), 97.1, 68.8, 52.3, 37.0, 36.7 (t, J = 24.6 Hz), 24.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -101.11 – -104.68 (m).

FTIR (neat) νmax: 3446, 3354, 3198, 2964, 2875, 1793, 1719, 1607, 1394, 1319, 1196, 1037, 1014, 909. 731, and 698 cm^{-1}.

HRMS (NSI) m/z: [M+H]+ calcd. for $C_{18}H_{23}O_5N_2F_2$, 385.1570; found, 385.1570.

3.5.6 Deprotection Procedures and Characterization Data



methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoic acid (2A):

To a stirring solution of methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (**2**) (190 mg, 0.5 mmol, 1 equiv) in THF/H_2O (3:2, 5 mL) was added LiOH (24 mg, 1.0 mmol, 2.0 equiv). The resultant solution was stirred until consumption of starting material was observed by thin layer chromatography. The reaction mixture was extracted once with ethyl acetate, and the organic extract was discarded. The aqueous phase was gently acidified with 0.1 M HCl to pH 4 and extracted with ethyl acetate (5 x 5 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated to provide the product (172 mg, 94% yield) as a clear, colorless crystalline solid.

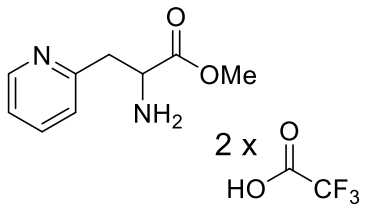
Mp: 164 °C (decomp.)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (dt, J = 5.0, 1.4 Hz, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.41 – 7.12 (m, 2H), 5.21 (dd, J = 7.9, 4.7 Hz, 1H), 3.93 (dd, J = 15.3, 7.9 Hz, 1H), 3.17 (dd, J = 15.3, 4.7 Hz, 1H), 1.45 (s, 18H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.68, 158.02, 152.08, 147.19, 138.60, 124.41, 122.43, 83.24, 58.25, 39.20, 27.94.

FTIR (neat) ν_{max}: 3456, 3068, 2970, 2930, 2853, 1748, 1708, 1366, 1108, 1062, and 778 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{27}O_6N_2$, 367.18636; found, 367.18591.



2-(2-ammonio-3-methoxy-3-oxopropyl)pyridin-1-ium ditrifluoroacetate (2B):

To a stirring solution of of methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (**2**) (190 mg, 0.5 mmol, 1 equiv) in dichloromethane (2 mL) was added trifluoroacetic acid (1.5 mL) dropwise. The resultant solution was allowed to continue stirring, and after 10 minutes consumption of starting material was observed by thin layer chromatography. The reaction mixture was concentrated directly by rotary evaporation. The solution was re-dissolved in dichloromethane and concentrated once more to quantitatively provide the product as a pale, yellow low-melting solid (203 mg, >99% yield).

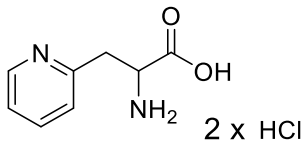
^{1}H NMR (300 MHz, D_3COD) δ 8.78 (dd, J = 5.7, 1.6 Hz, 1H), 8.44 (td, J = 7.9, 1.7 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.89 (td, J = 5.9, 2.8 Hz, 1H), 5.73 (s, 4H), 4.65 (t, J = 7.1 Hz, 1H), 3.77 (s, 3H), 3.69 (t, J = 7.2 Hz, 2H).

^{13}C NMR (75 MHz, D_3COD) δ 167.82, 159.86 (q, J = 37.9 Hz), 151.49, 144.91, 143.13, 127.44, 125.33, 117.61 (q, J = 289.1 Hz), 52.60, 51.59, 33.60, 26.25.

^{19}F NMR (282 MHz, D_3COD) δ -77.45.

FTIR (neat) ν_{max}: 2964, 2563, 2111, 1746, 1666, 1651, 1172, 1157, 1127, 836, 798, and 720 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_9H_{13}O_2N_2$, 181.09715; found, 181.09670.



2-amino-3-(pyridin-2-yl)propanoic acid dihydrochloride (2C):

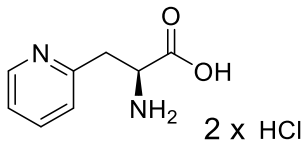
A 20-mL scintillation vial equipped with stir bar was charged with methyl 2-(di(*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoate (**2**) (190 mg, 0.5 mmol, 1 equiv), EtOH (5 mL) and 3N NaOH (5 mL), and the resultant solution was stirred until consumption of starting material was observed (~ 1 hour). The reaction mixture was acidified with 1M HCl and concentrated by rotary evaporation. The residue was reconstituted in EtOH, and precipitated NaCl was removed by vacuum filtration. The filtrate was concentrated under reduced pressure. Concentrated HCl (3 mL) was added dropwise to the residue and stirred 10 minutes. The mixture was concentrated directly to provide the product (119 mg, 96% yield) as a white crystalline solid.

^{1}H NMR (300 MHz, D_2O) δ 8.49 (d, J = 6.0 Hz, 1H), 8.32 (td, J = 8.0, 1.7 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.75 (dd, J = 7.7, 6.1 Hz, 1H), 4.34 (t, J = 7.4 Hz, 1H), 3.47 (d, J = 7.4 Hz, 2H).

^{13}C NMR (75 MHz, D_2O) δ 169.65, 149.60, 147.27, 141.42, 128.21, 126.15, 51.60, 33.20.

FTIR (neat) ν_{max}: 3399, 2780, 2934, 1702, 1567, 1477, 1403, 1367, 1243, 1139, 1102, 1101, 921, and 750 cm^{-1}.

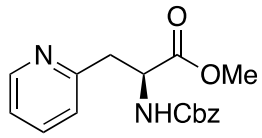
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_8H_{11}O_2N_2$, 167.08150; found, 167.08110.



(*S*)-2-amino-3-(pyridin-2-yl)propanoic acid dihydrochloride (42):

To a round bottom flask equipped with a stir bar was added **23** (20.2 mg), 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 (12.8, 98%) as a white solid. The physical properties and spectral data are consistent with the values of the racemate (**2C**) reported herein, with the exception of optical rotation.

$[\alpha]_D^{20}$ +31.7 (*c* 0.1, 1 M HCl) (lit.,[31] +46.0 (*c* 0.1, 1 M HCl))



methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(pyridin-2-yl)propanoate (42A):

To a round bottom flask equipped with a stir bar was added **24**, Et_2O (5 mL), and MeOH (5 mL). The reaction was placed under nitrogen atmosphere then cooled to 0 °C. (Trimethylsilyl)diazomethane solution (2.0 M in ether, 80 μL, 0.16 mmol, 2.0 equiv) was added dropwise via syringe and the reaction was warmed to room temperature and stirred for 30 minutes. The reaction was quenched with AcOH (2 mL) then concentrated by rotary evaporation. The residue was dissolved in saturated aqueous sodium bicarbonate (1 mL) and THF (1 mL). The

[31] Anaïs F. M. Noisier, Craig S. Harris, and Margaret A. Brimble *Chem. Commun*., **2013**, *49*, 7744.

solution was set to stir and chilled to 0 °C. Benzyl chloroformate (12.5 μL, 0.09 mmol, 1.1 equiv) was added dropwise via syringe, and the reaction was warmed to room temperature and stirred until HPLC indicated the starting material had been consumed. The reaction was concentrated to remove THF then diluted with water (1 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 preparative HPLC to afford the product as a colorless oil. Chiral HPLC analysis (OD-H, 15% IPA/hexanes, 1.0 mL/min, 254 nm) indicated 97% ee for the major enantiomer (t_R (major) = 14.949 min, t_R (minor) = 21.299 min).

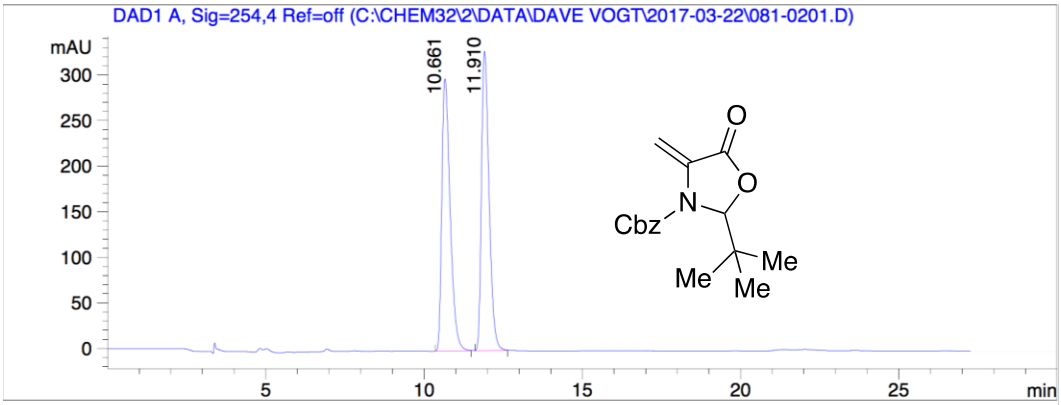
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 4.7 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.39 – 7.27 (m, 5H), 7.15 – 7.09 (m, 2H), 6.30 (d, *J* = 8.2 Hz, 1H), 5.15 – 5.05 (m, 2H), 4.76 (dt, *J* = 8.4, 5.3 Hz, 1H), 3.68 (s, 3H), 3.36 (dd, *J* = 14.9, 5.7 Hz 1H), 3.28 (dd, *J* = 14.9, 4.7 Hz 1H).

^{13}C NMR (125 MHz, Chloroform-*d*) δ 172.19, 157.10, 156.18, 149.30, 136.71, 136.52, 128.59, 128.22, 128.20, 123.81, 121.99, 67.00, 53.48, 52.46, 39.06.

FTIR (neat) ν_{max}: 3333, 3032, 2951, 1716, 1593, 1507, 1436, 1340, 1210, 1050, 911, 752, and 670 cm^{-1}.

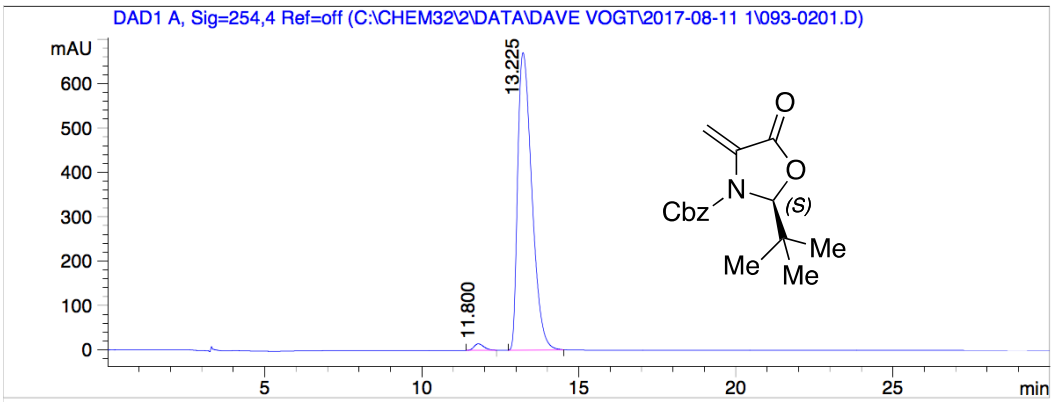
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{19}O_4N_2$, 315.13393; found, 315.13349.

3.5.7 Chiral HPLC Data



#	Compound Name	Amount	Resp.	Resp.%	Exp.RT	Meas.RT
1		0.000	5.459e3	49.955	0.000	10.661
2		0.000	5.469e3	50.045	0.000	11.910
Totals:		0.000				

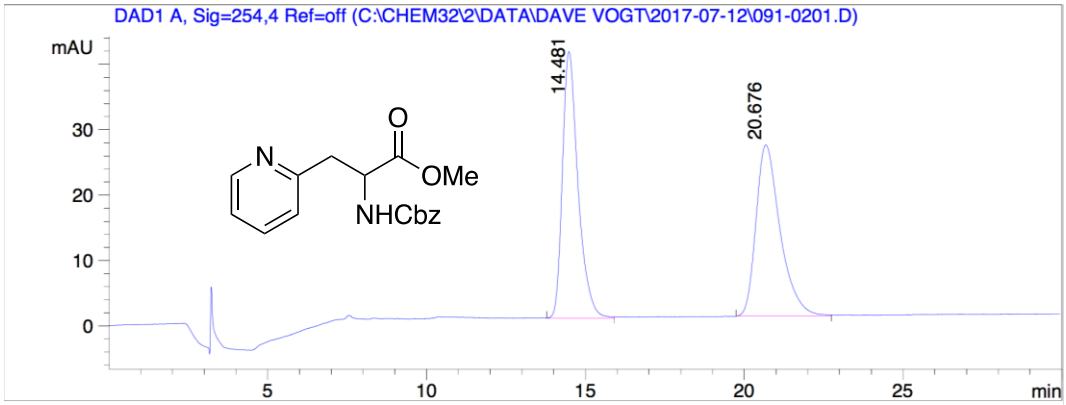
Figure S3.1. Chiral HPLC of Racemic Dha



This is a result compounds table. Use the footer button in the table format dialog box to define the summations in the last table line.

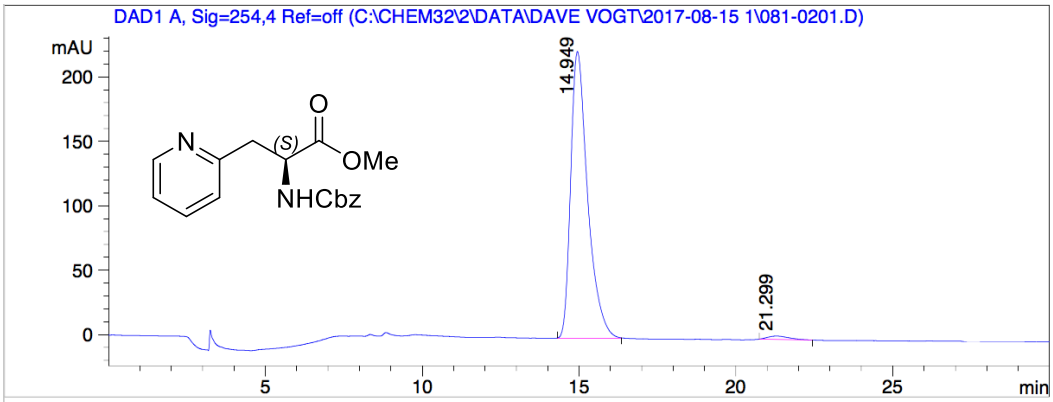
#	Compound Name	Amount	Resp.	Resp.%	Exp.RT	Meas.RT
1		0.000	326.194	1.530	0.000	11.800
2		0.000	2.099e4	98.470	0.000	13.225
Totals:		0.000				

Figure S3.2. Chiral HPLC of Enantioenriched Dha



#	Compound Name	Amount	Resp.	Resp.%	Exp.RT	Meas.RT
1		0.000	1.399e3	50.170	0.000	14.481
2		0.000	1.389e3	49.830	0.000	20.676
Totals:		0.000				

Figure S3.3. Chiral HPLC of Racemic Cbz-pyridylalanine methyl ester



This is a result compounds table. Use the footer button in the table format dialog box to define the summations in the last table line.

#	Compound Name	Amount	Resp.	Resp.%	Exp.RT	Meas.RT
1		0.000	8.375e3	98.471	0.000	14.949
2		0.000	130.034	1.529	0.000	21.299
Totals:		0.000				

Figure S3.4 Chiral HPLC of Enantioenriched Cbz-pyrdylalanine methyl ester

3.5.8 Stern-Volmer Fluorescence Quenching Experiments:

All fluorescence measurements were recorded using a Horiba Scientific Dual-FL Fluorometer. Quenching studies were conducted in DMSO:H2O (5:1) at 20 ±0.5 °C (Peltier temperature controller) with an $[Ir(ppy)_2(dtbbpy)]PF_6$ concentration of 5 µM. Raw fluorescence intensity was measured at λ = 591 nm after excitation at λ = 450 nm in a quartz cuvette with a path length of 1 cm. Measurements using Hantzsch ester, dehydroalanine, or 2-bromopyridine as quenchers were taken in triplicate at concentrations of 0, 50, 100, 250, and 500 µM. At quencher concentration of 0 µM, additional duplicate measurements were collected prior to successive quenchers to maintain accuracy. SternVolmer plots were generated using Igor Pro 7; data points were fit with a linear trend line.

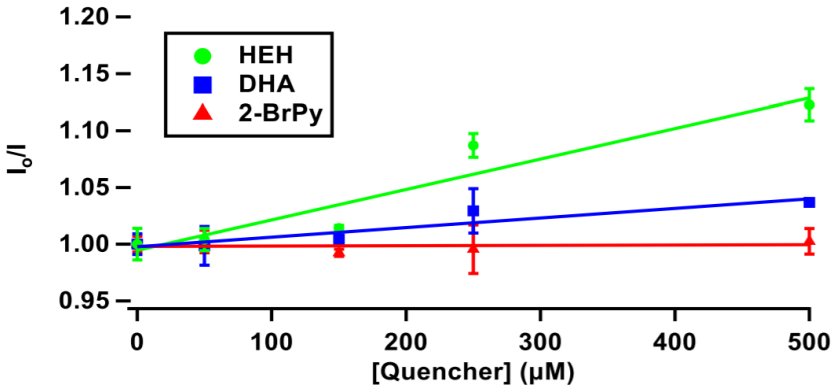


Figure S3.5 Overlay of Stern-Volmer Plots

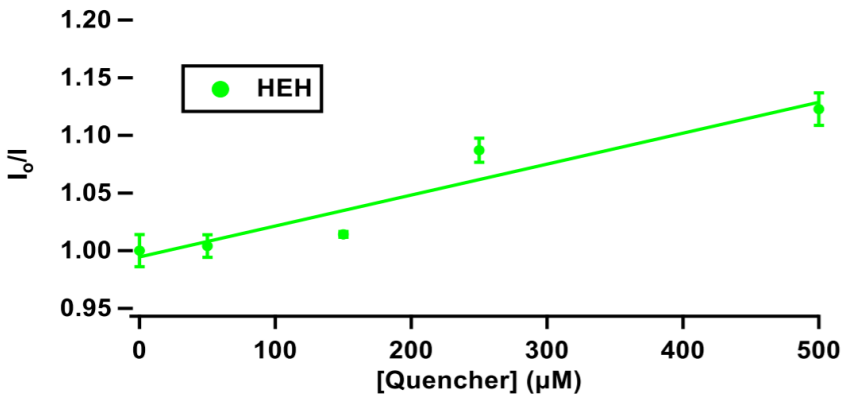


Figure S3.6 Stern-Volmer Quenching Plot of Hantzsch Ester

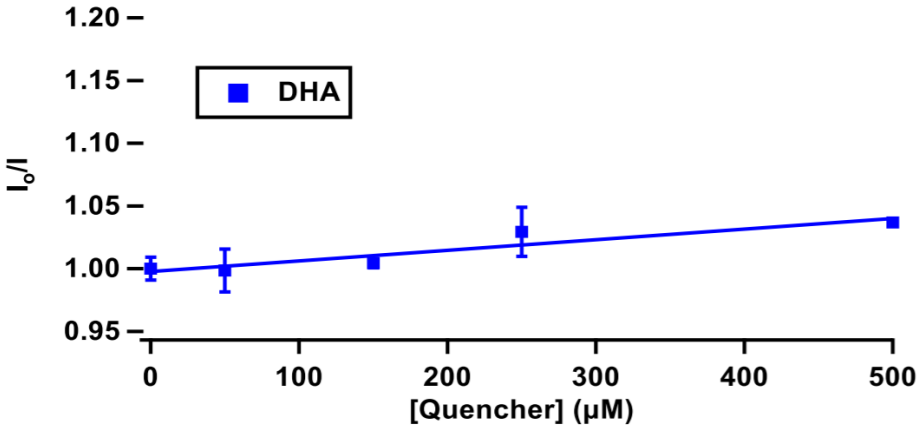


Figure S3.7 Stern-Volmer Quenching Plot of Dehydroalanine

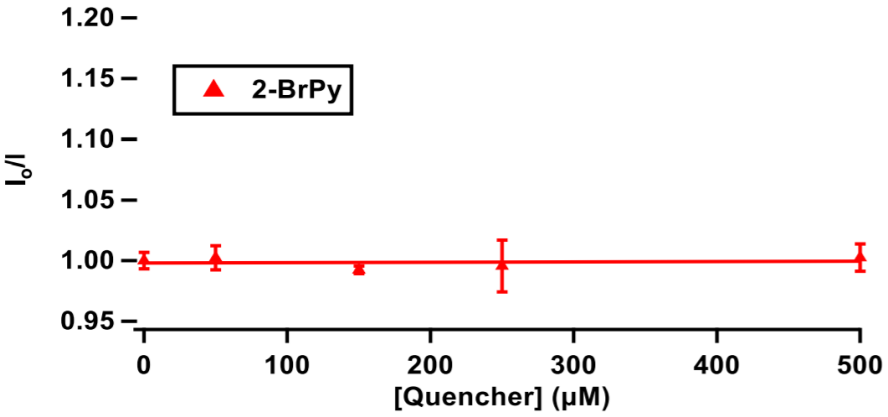


Figure S3.8 Stern-Volmer Quenching Plot of 2-bromopyridine

[HEH] (μM)	1	2	3	avg	stdev	I_o/I	error
0	5966.1219	5849.4855	-	5907.8037	82.4743	1.0000	0.0140
50	5819.8148	5929.6318	5902.7293	5884.0586	57.2398	1.0040	0.0098
100	5841.5493	5819.6902	5813.9702	5825.0699	14.5553	1.0142	0.0025
250	5374.5285	5468.2221	5461.4238	5434.7248	52.2422	1.0870	0.0104
500	5200.5652	5253.6675	5331.9516	5262.0614	66.0942	1.1227	0.0141

[DHA] (μM)	1	2	3	avg	stdev	I_o/I	error
0	5839.3979	5914.3043	5903.3400	5885.6807	40.4553	1.0519	0.0072
50	6095.6538	6197.9486	6307.0152	6200.2059	105.6987	0.9985	0.0170
100	6173.1678	6181.4130	6138.4126	6164.3311	22.8216	1.0043	0.0037
250	6057.7748	6100.8092	5884.9329	6014.5056	114.2576	1.0294	0.0196
500	5968.5599	5976.2475	5967.5891	5970.7988	4.7436	1.0369	0.0008

[2-BrPy] (μM)	1	2	3	avg	stdv	I_0/I	error
0	6151.0503	6231.0219	-	6191.0361	56.5485	0.9507	0.0087
50	5805.9303	5890.0415	5918.6204	5871.5308	58.5812	1.0024	0.0100
100	5951.2881	5923.7698	5915.9019	5930.3199	18.5802	0.9925	0.0031
250	5829.0025	5848.4549	6057.4723	5911.6432	126.6656	0.9956	0.0213
500	5840.9751	5825.5125	5946.4111	5870.9662	65.7930	1.0025	0.0112

Figure S3.9. Measured Fluorescence Intensities at λ = 591 nm (counts)

3.5.9 α-Deuteration With D_2O as Solvent:

Following the general procedure, the reaction of 2-bromopyridine (32 mg, 0.20 mmol, 1 equiv), methyl 2-(di(tert-butoxycarbonyl)amino)acrylate (120 mg, 0.40 mmol, 2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (2.1 mg, 0.0021 mmol, 0.01 equiv) and Hantzsch ester (76 mg, 0.30 mmol, 1.3 equiv) provided the product (72 mg, 94% yield) as white solid after purification by flash column chromatography (5% – 40% ethyl acetate/hexanes). Integration of the alpha proton 1 H NMR signal was used to determine the percent of deuterium incorporation (94% D).

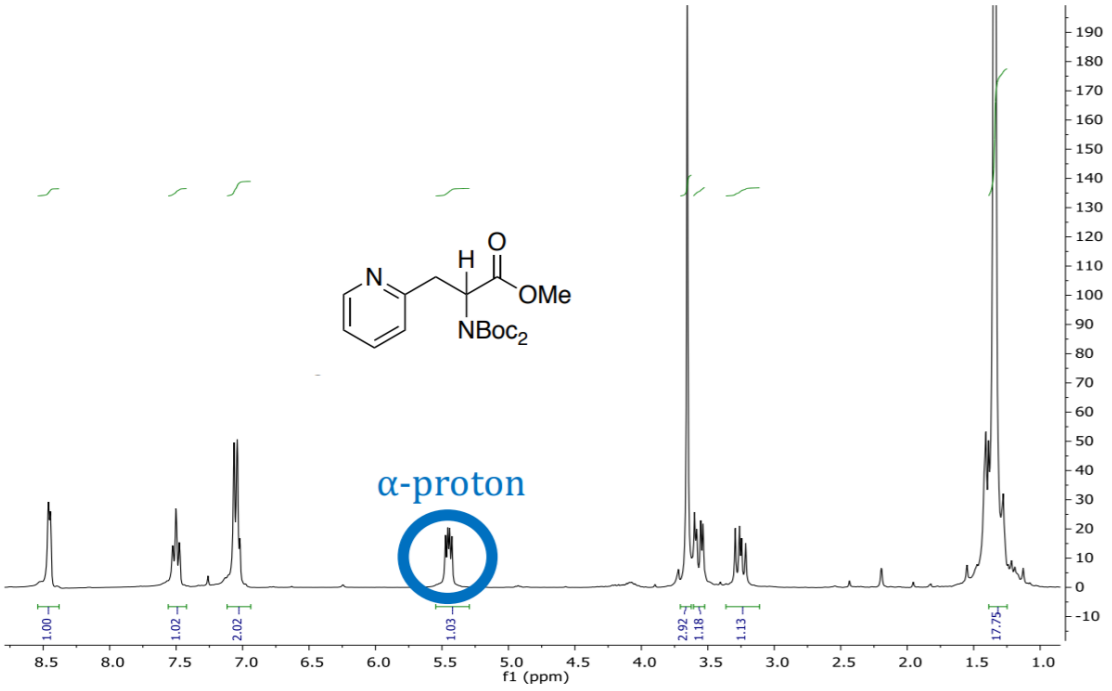


Figure S3.10. ^{1}H NMR: α-protio-pyridylalanine ester

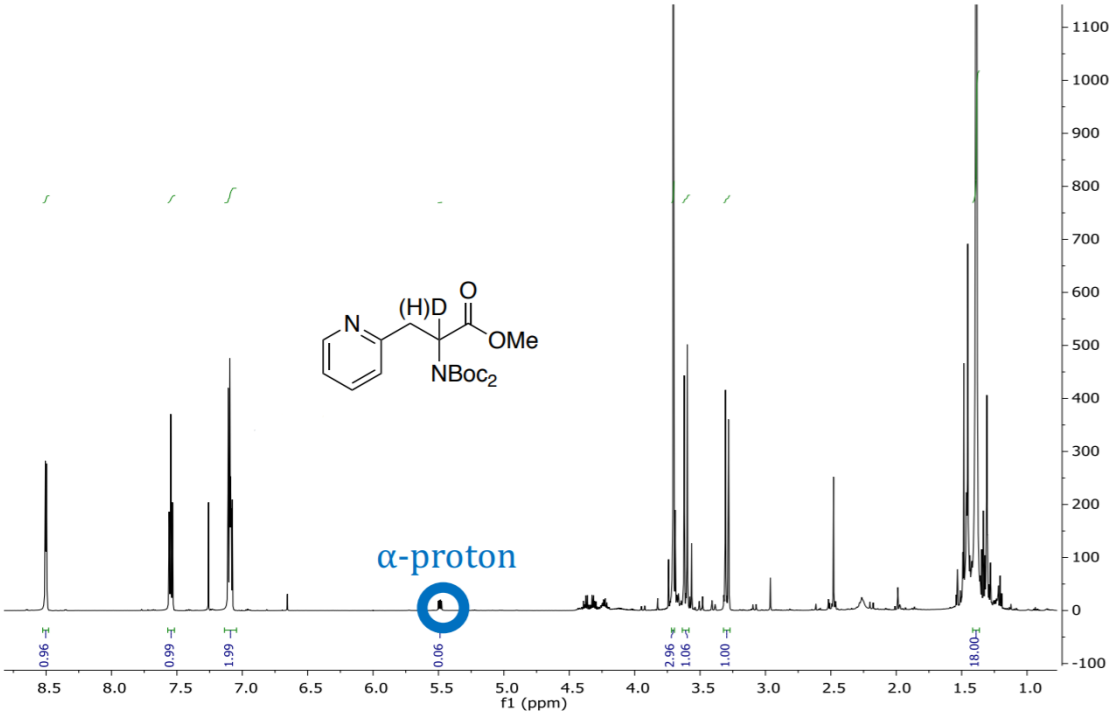


Figure S3.11. ^{1}H NMR: α-deutero-pyridylalanine ester

Chapter 4

Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides

Adapted 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.

C. J. Pratt contributed the scope of α-amino radical conjugate addition to chiral DHA radical accepto and the preparation of peptide 20.

4.1 Abstract

A robust method for the direct addition of unactivated tertiary amines to dehydroalanine (Dha) derivatives has been developed. This method, which is driven by a photoredox catalyst and light, operates through α C–H functionalization mechanism, where α-amino radical formation triggers highly chemoselective radical conjugate addition. This mild protocol effectively activates highly complex amine structures for coupling with a range of Dha substrates to furnish unnatural amino acids and peptides.

4.2 Introduction

Chemical modification of biomolecules is an important challenge in modern organic synthesis. Elegant biochemical strategies that involve enzymatic ligation systems[1] or programmed incorporation of non-natural amino acids[2] have been developed. These methods, in conjunction with biorthogonal "click" reactions,[3,4] play a central role in nonnatural protein and/or peptide synthesis. In addition, there are many tremendously impactful chemical approaches that leverage the native reactivity of specific residues (e.g., cysteine, lysine, N-terminal amine) to achieve bioconjugation.[5] However, the abundance of nucleophilic species, the requirement for aqueous media, and strict thermal inflexibility are daunting barriers in the translation of other reaction

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modes to synthetic peptide manipulation. Recent advances involving olefin metathesis,[6,7] nucleophilic aromatic substitution (SNAr),[8,9] and transition-metal mediated processes[10] have yielded synthetic methods that operate in very complex environments with impressive efficiency and selectivity.

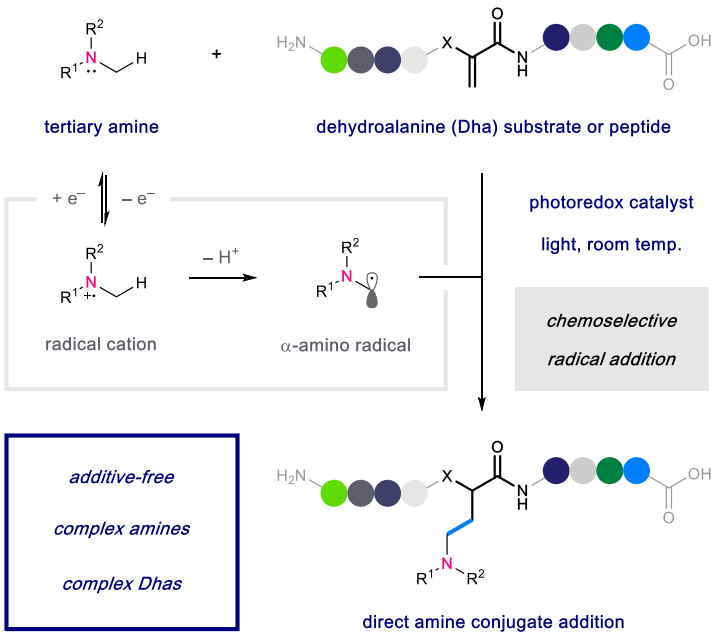

Figure 4.1. Strategy for direct conjugate addition of unactivated amines to Dha.

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Radical intermediates are well-known for their unique propensities to chemoselectively engage olefinic species in polar, heteroatom-rich environments. MacMillan has shown the remarkable ability of photoredox catalysis to perform selective activation of C-terminal carboxylates.[11,12] Upon single electron oxidation and decarboxylation, the resulting radicals react with conjugate acceptors in macrocyclization processes or site-selective intermolecular ligations with very high efficiency. Davis[13] and Park[14] independently demonstrated that primary alkyl radicals (formed through stoichiometric reduction of the corresponding halides) undergo radical conjugate addition to dehydroalanine (Dha), thereby introducing a new strategy for backbone alteration through C−C bond formation. The power of this approach is underscored by the fact that numerous methods exist for the efficient production of Dha residues, even in intact proteins.[15] We describe the development of an alternative strategy for site-selective peptide conjugation that utilizes unactivated tertiary amines as substrates that effectively engage Dha, through a photoredox C−H functionalization mechanism (illustrated in Figure 1).

Photochemical activation of amine substrates, through the formation of α-amino radicals, has emerged as a powerful synthetic pathway. Building on the pioneering work of Mariano and

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Pandey,[16,17] in addition to studies by MacMillan,[18] Reiser,[19] Nishibayashi,[20] Yoon[21,22] and others[23] have demonstrated that α-amino radicals, generated by visible-light photoredox catalysis,[24,25] can be utilized in a diverse array of powerful synthetic transformations. These radical intermediates engage a range of olefin substrates, where the most general systems involve the reaction of functionalized amine substrate classes (e.g., α-silylamines, amino acids, or aminoalkylboronates) with electron-poor olefins. Unfunctionalized amine derivatives also serve as precursors to these radical intermediates, either through direct hydrogen atom abstraction[26] or sequential single-electron oxidation/C−H deprotonation[27] Importantly, asymmetric amine radical conjugate addition

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processes have recently been described by Yoon[22], Melchiorre[23d], Kang,[28] Gong,[29] and Meggers[30] using anilines or amines containing fragmentable groups. Here, we demonstrate that a wide range of unactivated, complex amine subtypes undergo reaction with Dha substrates with exceptional efficiency. This method operates under mild conditions, giving rise to unnatural amino acid derivatives with complete diastereocontrol. Furthermore, the highly chemoselective nature of this process enabled the development of a new system for peptide functionalization.

4.3 Results and discussion

To evaluate the feasibility of this amine−Dha conjugate addition, we studied the coupling of N,N-dimethylaniline and the Karady−Beckwith chiral Dha substrate[31] (see the Supporting Information (SI) for detailed reaction development). Under irradiation by a commercial blue LED in acetonitrile, the iridium-based photoredox catalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)^+$ mediates the desired amine conjugate addition with excellent efficiency. According to the mechanistic blueprint that is illustrated in Figure 4.1, oxidative α-amino radical formation is followed by radical conjugate addition to the Dha substrate. After reduction of the resulting radical species, protonation of the corresponding enolate delivers the desired product. Inspired by a report by Molander,[32] we elected to utilize an additive survey to rapidly assess the chemoselectivity of the outlined process. The outlined catalytic amine conjugation was tolerant of indole, phenol, sodium propionate, and

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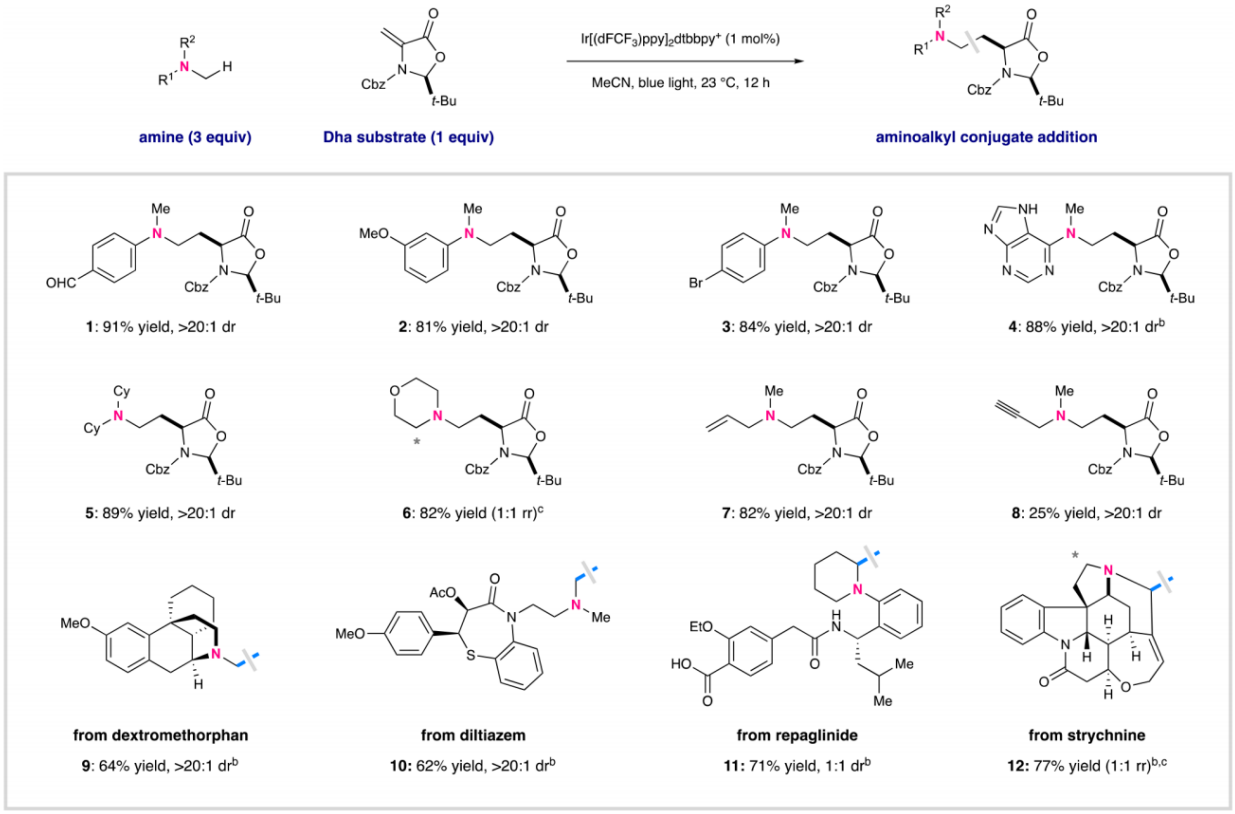
imidazole, (as models for tryptophan, tyrosine, carboxylates, and histidine, respectively). This process also functioned with added butyl mercaptan (as a proxy for cysteine), although thiol conjugate addition was competitive.

We investigated the scope of the amine substrate, again employing the Karady−Beckwith Dha as a coupling partner. As shown in Table 4.1, a wide range of aniline derivatives with varied electronic properties smoothly undergo activation and subsequent aminoalkyl conjugate addition, giving the corresponding unnatural amino acid derivatives with complete selectivity for the cis-isomer (in accord with previous findings;[31c] see the SI for deprotection conditions, analysis of

Table 4.1. Amine C−H Activation/Conjugate Addition to Chiral Dehydroalanine (Dha): Tertiary Amine Scope



enantiopurity). We found that aniline substrates that contain electron-withdrawing groups are especially active under these conditions. For example, the benzaldehyde function, which is an important biorthogonal coupling unit, was cleanly retained, and the desired adduct **1** was produced in 91% yield. The 3- methoxy-substituted aniline was smoothly transformed to oxazolidinone **2** (81% yield), although the corresponding ortho- or para-methoxyaniline derivatives were unreactive, which is analogous to previous findings. As expected, the aryl bromide was preserved under these conditions giving rise to **3** in 84% yield, containing a handle for further functionalization. Importantly, the arylamine unit is not required for effective coupling with Dha. Specifically, methyldicyclohexylamine reacted to give **5** as the exclusive product, but the use of Nmethylmorpholine gave rise to three isomeric products. In this case, the major product (**6**, formed as a single diastereomer) resulted from methyl activation, and two minor products came from addition from either prochiral face of the endocyclic α-methylene position. We observed selective formation of allylic and propargylic amines **7** and **8** (in 82% and 25% yield, respectively), although conversion of the clickable alkyne substrate was low.

Encouraged by these results, we applied this system to the direct functionalization of complex bioactive tertiary amines. Selective activation of the N-methyl groups in the morphinan dextromethorphan and calcium channel blocker diltiazem occurred under standard conditions, giving rise to **9** and **10** in acceptable yields (64% and 62%, respectively). Regioselective reaction of the N-arylpiperidine repaglinide gave two diastereomers in equal amounts (71% combined yield), arising from nonselective methylene activation. Finally, standard conditions smoothly delivered **12** from the complex alkaloid strychnine. In this case, activation of the tertiary amine led to regioisomeric products (indicated by the asterisk in Table 4.1) that arose from the addition

of the olefin to the convex face of both the D and E rings. Unless otherwise indicated, the shown products were formed with complete regiocontrol, as determined by NMR and HPLC analysis.

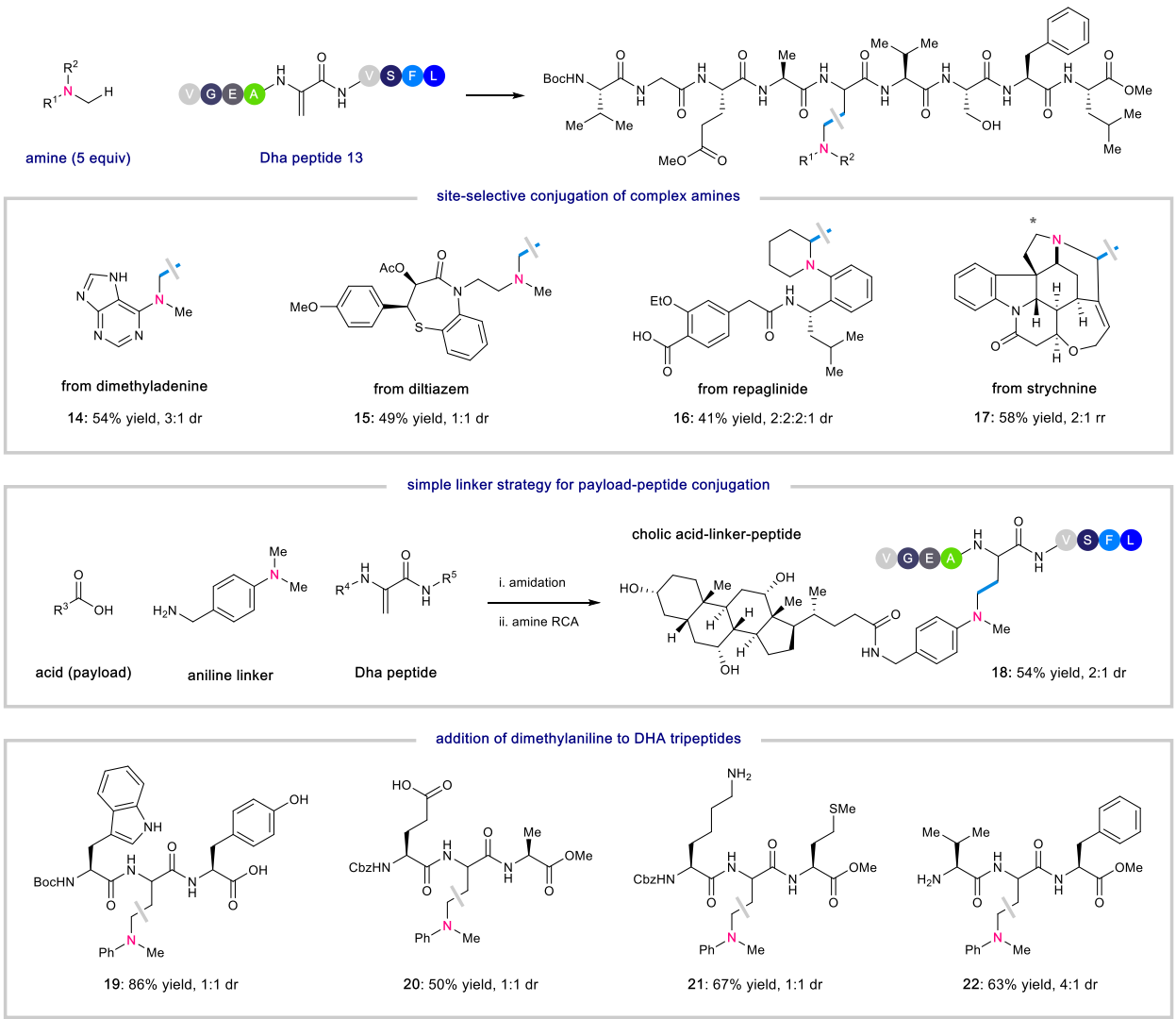
Next, we investigated the direct addition of complex amines to Dha peptides, and the results are shown in Table 4.2. We prepared Dha peptide **13** using standard solution-phase peptide-coupling procedures and subsequent elimination of the internal cysteine thiol. Under slightly modified conditions (5.0 equiv amine, 1 mol % photocatalyst, blue light, DMSO, room temperature), effective conjugate addition of amine substrates was observed by HPLC. Regiochemical assignments (i.e., amine activation sites) were made in analogy to RCA adducts from Table 4.1, and yields refer to isolated yields of diastereomeric mixtures that were obtained by preparative HPLC. Site-repaglinide could be directly appended to this peptide backbone with good efficiency (**15**: 49% yield, 1:1 diastereomeric ratio (dr); **16**: 41% yield, 2:2:2:1 dr). The strychnine−peptide conjugate **17** was furnished as an inseparable mixture of regioisomers and diastereomers. Again, C−C bond formation occurred at both of the α-amino methylene positions within this natural product. Importantly, exclusive activation of the desired aniline (or amine) was observed and a range of acidic or otherwise challenging groups were well-tolerated.

This mild tertiary amine-Dha conjugate addition protocol is also useful for site-selective delivery of small molecules to peptides using a linker-based strategy. More specifically, we envision a system where installation of a tertiary amine (or aniline) linker to a chemical scaffold (payload) would enable site-selective delivery to a peptide backbone. As a first example, cholic acid was transformed to the corresponding 4-(dimethylamino)benzylamide and subjected to standard reaction conditions to give the ternary peptide-linker-drug adduct **18** in good yield (54%, 2:1 dr). These results demonstrate the uniquely effective ability to achieve selective C−H functionalization in the presence of other weak C−H bonds, acidic groups, hydrolytically labile

moieties, oxidizable elements, electron-rich aromatics, and heterocycles.

To further examine the tolerance of this process to other potentially reactive residues, we constructed a small series of Dha-containing tripeptides. Reaction of these substrates with dimethylaniline gave rise to products **19**–**22**. Specifically, **19** was produced in 86% yield from

Table 4.2. Amine C–H Activation/Conjugate Addition to Dha Peptides: Substrate Scope



Boc-Trp-Dha-Tyr-OH, where the desired alkylamine conjugate addition was not significantly impacted by the indole, phenol, or terminal carboxylate. Also effective was Cbz-Glu-Dha-Ala-OMe under this protocol, which gave rise to **20** (50% yield, 1:1 dr), further exemplifying chemoselective aniline activation (in the presence of an unprotected side-chain carboxylate). **21** was efficiently prepared from Cbz-Lys-Dha-Met-OMe under slightly acidic conditions (such that the alkylamine was preferentially protonated, allowing for aniline activation), thus preserving the unprotected side chain amine and oxidizable thioether groups (67% yield, 1:1 dr). Finally, reaction of H_2N-Val-DhaPhe-OMe (again, as the corresponding trifluoroacetic acid salt) afforded **22**, where conjugation was unaffected by unprotected N-terminal amine, and slightly higher diastereoselectivity was observed (63% yield, 4:1 dr).

4.4 Conclusion

We have described a robust catalytic system for the direct union of a wide range of tertiary amine structures with Dha derivatives. This photoredox system is highly chemoselective. It operates effectively at room temperature and requires light as the only stoichiometric additive. Consequently, we have shown that this reactivity can be applied in the synthesis of highly complex unnatural amino acids and peptides with good efficiency. Preliminary studies indicate that this protocol can be conducted in aqueous solvent mixtures and at high dilution (olefin concentration = 0.001 M, see the SI for details). However, we recognize that the lack of diastereocontrol is a primary limitation of this method in its current form. Further mechanistic studies, designs aimed at achieving diastereoselectivity, and the development of related processes are ongoing in our laboratory.

4.5 Experimental Information

4.5.1 General Information

General Reagent 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, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$[33] and $[Ir(ppy)_2(dtbbpy)]PF_6$[34] were prepared according to literature procedures. 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.[35]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[36,37]. 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.

[33] Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, Jr., R. A.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater*. 2005, 17, 5712–5719.

[34] Lowry, M. S.; Hudson, W. R.; Pascal, R. A.; Bernhard, S. Accelerated Luminophore Discovery through Combinatorial Synthesis. *J. Am. Chem. Soc*. 2004, 126, 14129.

[35] Chapmann, C. J.; Matsuno, A.; Frost, C. G.; and Willis, M. C. Site-selective modification of peptides using rhodium and palladium catalysis: complementary electrophilic and nucleophilic arylation. *Chem. Commun*. 2007, 0, 3903-3905.

[36]Adams, L. A.; Aggarwal, V. K.; Bonnert, R. V.; Bressel, B.; Cox, R. J.; Shepherd, J.; de Vicente, J.; Walter, M.; Whittingham, W. G.; and Winn, C. L. Diastereoselective Synthesis of Cyclopropane Amino Acids Using Diazo Compounds Generated in Situ. J. Org. Chem. 2003, 68, 9433.

[37] Aycock, R. A.; Vogt, D. B.; Jui, N. T. A practical and scalable system for heteroaryl amino acid synthesis. *Chem. Sci.* 2017, 8, 7998-8003.

General Analytical Information:

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 ^1H NMR and 77.23 ppm for ^{13}C NMR; $(CD_3)_2CO$: 2.05 ppm for ^1H NMR and 29.84, 206.26 ppm for ^{13}C NMR; CD_3OD: δ 3.31 ppm for ^1H 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 ^1H 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.

4.5.2 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.

4.5.3 Optimization Details

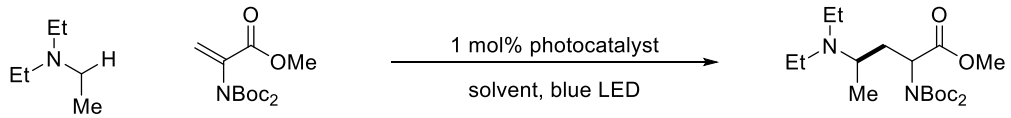
Optimization Procedure:

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 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.

Optimization Table:

Table S4.1. 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

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.

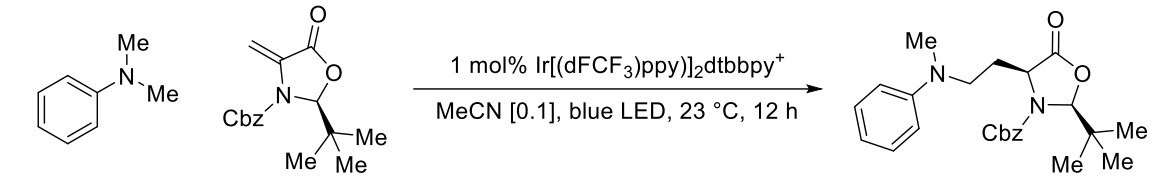
Deviation Procedure when DMSO is used as Solvent:

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

Deviation Table:

Table S4.2. Results of yield of amine-Dha conjugate addition product caused by deviations from optimized conditions.

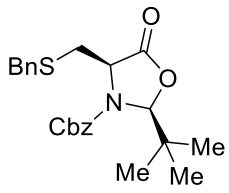


N,N-dimethylaniline chiral Dha amine-Dha conjugate addition

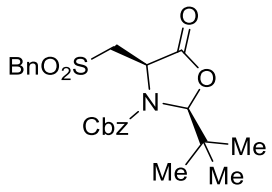
entry	deviation from optimal conditions[a]	chiral Dha remaining	yield[b]
1	none	0%	81%
2	without light	100%	0%
3	without catalyst	100%	0%
4	1 eqv. indole	0%	92%
5	1 eqv. phenol	60%	28%
6	1 eqv. sodium propionate	0%	81%
7	1 eqv. imidazole	0%	87%
8	1 eqv. butyl mercaptan	0%	31%[c]
9	1 eqv. acetic acid	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), $Ir[(dFCF_3)ppy)]_2dtbbpy$-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.

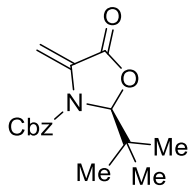
4.5.4 Preparation of Starting Materials



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 ^{1}H 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.

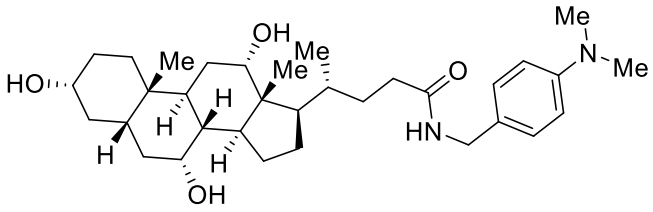


benzyl (2S,4R)-4-((benzylsulfonyl)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxy-late: To a round bottom flask equipped with a stir bar was added benzyl (2S,4R)-4-((benzylthio)methyl)-2-(tert-butyl)-5-oxooxazolidine-3-carboxylate (6.3 g, 15.25 mmol, 1 equiv), *meta*-chloroperoxybenzoic acid (6.6 g, 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.

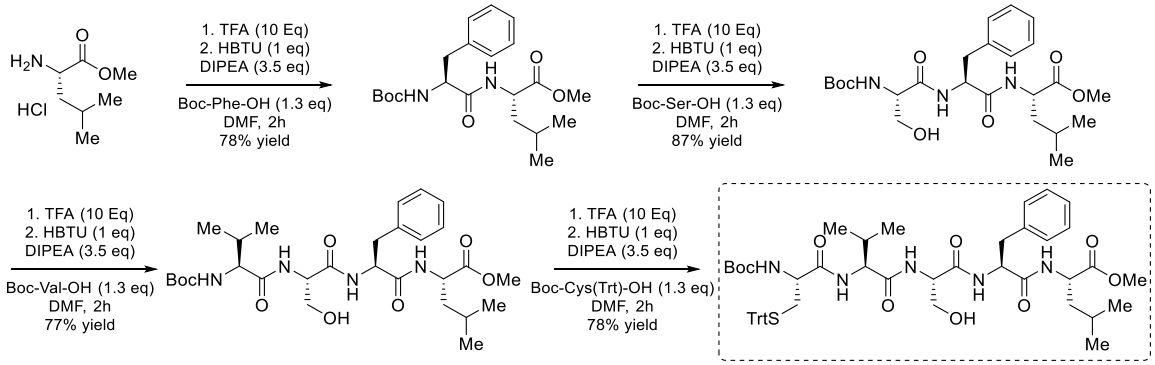
^{1}H NMR (600 MHz, Methanol-d_4) δ 7.12 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 4.29 – 4.13 (m, 2H), 3.92 (d, J = 3.1 Hz, 1H), 3.78 (q, J = 3.0 Hz, 1H), 3.36 (tt, J = 11.2, 4.3 Hz, 1H), 2.88 (s, 6H) 2.32 – 2.19 (m, 3H), 2.18 – 2.08 (m, 1H), 2.01 – 1.91 (m, 2H), 1.90 – 1.76 (m, 4H), 1.76 –

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}.

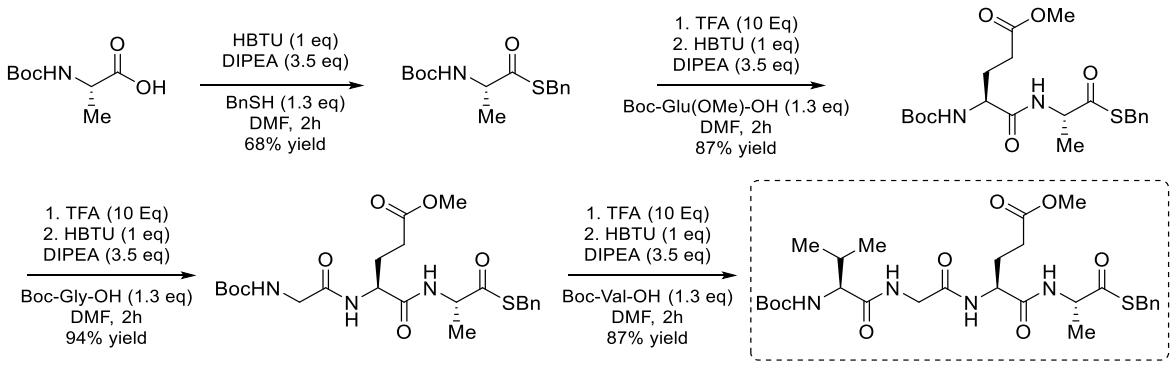
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{33}H_{53}O_4N_2$, 541.4000; found, 541.4002.



Scheme S4.1. 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.

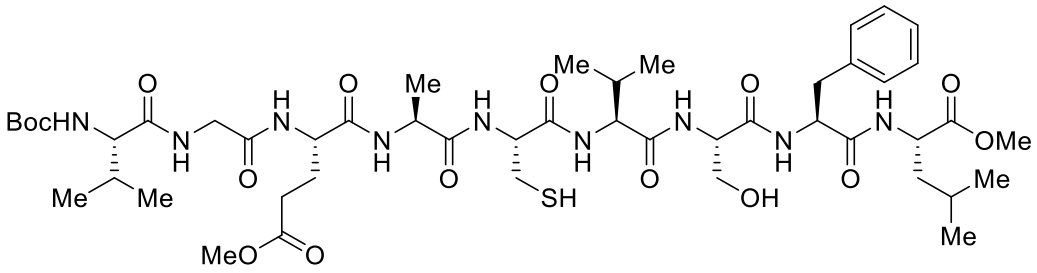


Scheme S4.2. Boc-Val-Gly-Glu(OMe)-Ala-SBn**:** prepared by sequential peptide coupling and deprotection steps (beginning from Boc-Ala-OH) following general procedure D. The series of reactions provided the product as a white crystalline solid (4.1 g) after passing through a short pad of silica (100 % 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.



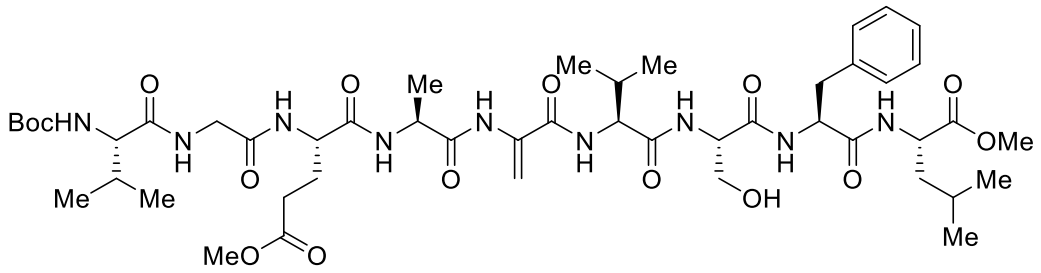
Boc-Val-Gly-Glu(OMe)-Ala-Cys-Val-Ser-Phe-Leu-OMe:

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.

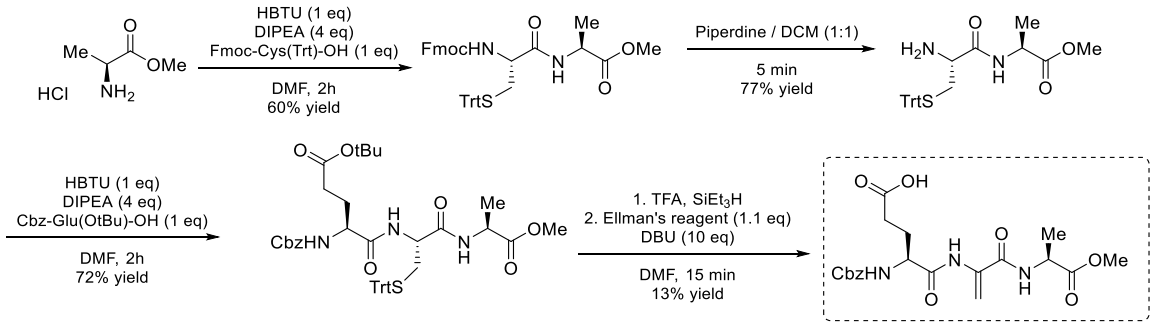


Boc-Val-Gly-Glu(OMe)-Ala-DHA-Val-Ser-Phe-Leu-OMe:

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).

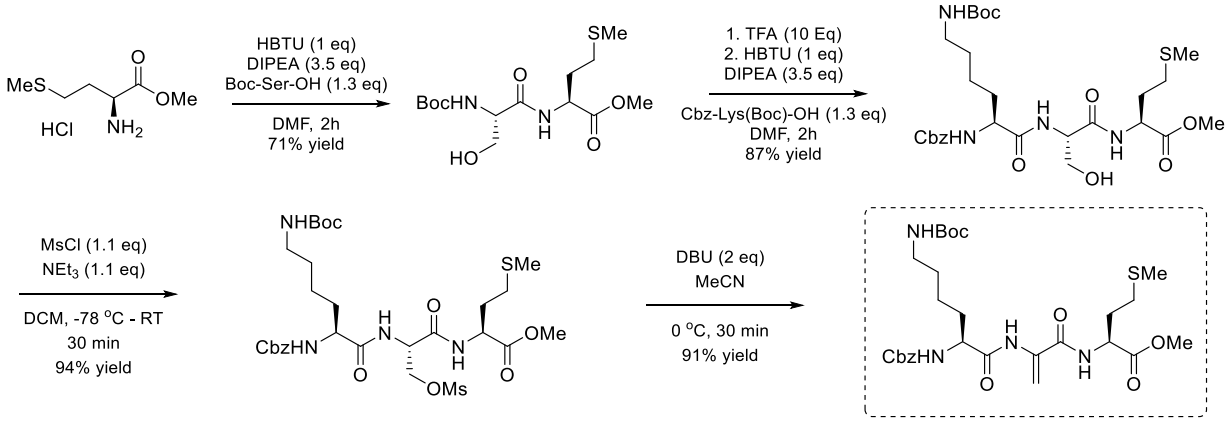
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{48}H_{75}O_{15}N_9Na$, 1040.5275; found, 1040.5261.



Scheme S4.3. 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.

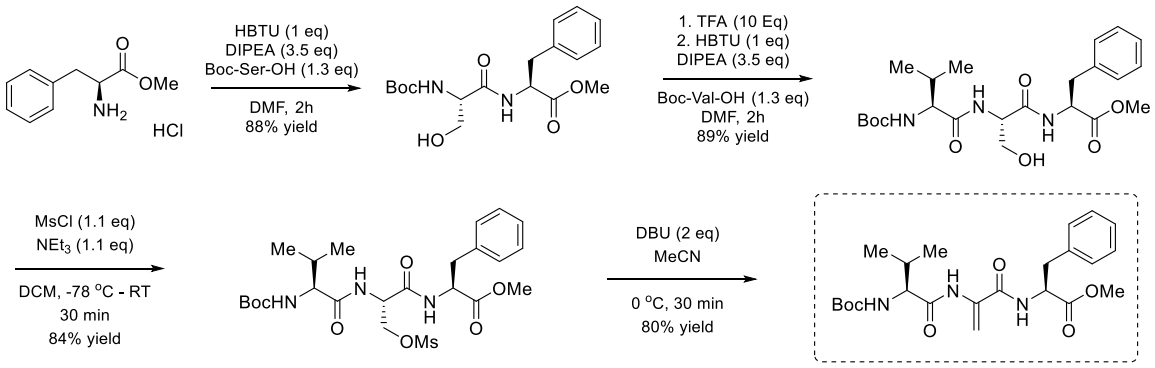


Scheme S4.4. Cbz-Lys(Boc)-Dha-Met-OMe: prepared by sequential peptide coupling and deprotection steps (beginning from the H_3N-Met-OMe • HCl) following general procedure D to afford Cbz-Lys(Boc)-Ser-Met-OMe. To a stirring solution of Cbz-Lys(Boc)-Ser-Met-OMe (312 mg, 0.5 mmol, 1 equiv) in DCM (20 mL) 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.

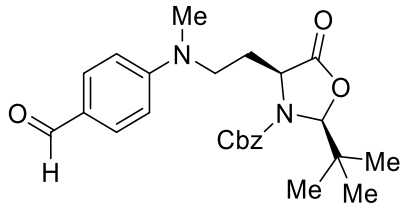


Scheme S4.5. Boc-Val-Dha-Phe-OMe: prepared by sequential peptide coupling and deprotection steps (beginning from the H_3N-Phe-OMe • HCl) following general procedure D to afford Boc-Val-Ser-Phe-OMe. To a stirring solution of Boc-Val-Ser-Phe-OMe (500 mg, 1.1 mmol, 1 equiv) in DCM (25 mL) at -78 °C was 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.

4.5.5 Procedure and Characterization Data



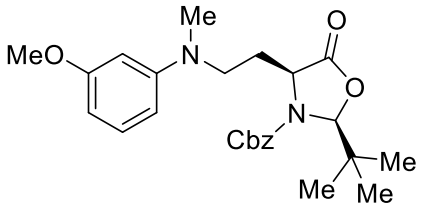
1: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (59.7 mg, 0.2 mmol, 1 equiv), 4-(dimethylamino)benzaldehyde (89.4 mg, 0.6 mmol, 3 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.1 mg, 0.0020 mmol, 0.01 equiv) provided the product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



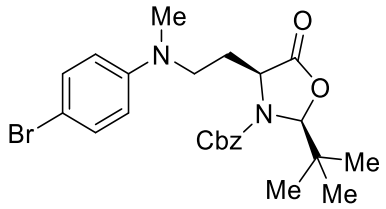
2: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (57.8 mg, 0.2 mmol, 1 equiv), 3-methoxy-N,-dimethylaniline (92.1 mg, 0.6 mmol, 3 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.3 mg, 0.0020 mmol, 0.01 equiv) provided the product 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.



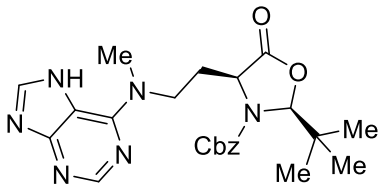
3: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (60 mg, 0.2 mmol, 1 equiv), 4-bromo-*N*,*N*-dimethylaniline (123 mg, 0.6 mmol, 3 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.4 mg, 0.002 mmol, 0.01 equiv) provided the product 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.



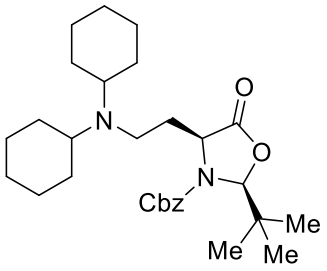
4: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (28.9 mg, 0.1 mmol, 1 equiv), N,N-dimethyladenine (270 ml, 0.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (1.1 mg, 0.001 mmol, 0.01 equiv) provided the product as a single 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.



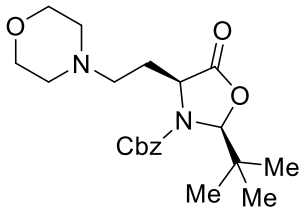
5: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), N-cyclohexyl-N-methylcyclohexanamine (130 μL, 0.6 mmol, 3.0 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.2 mg, 0.002 mmol, 0.01 equiv) provided the 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.



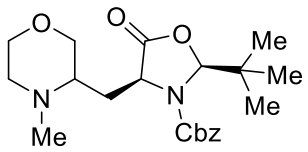
6: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), 4-methylmorpholine (66 μL, 0.6 mmol, 3 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.2 mg, 0.002 mmol, 0.01 equiv) provided the product as a single 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).

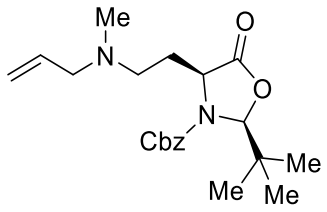
For the mixture of diastereomers:

^{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.



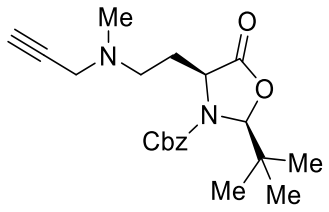
7: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), N,N-dimethylallylamine (71 μl, 0.6 mmol, 3.0 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.2 mg, 0.0020 mmol, 0.01 equiv) provided the product as a 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.



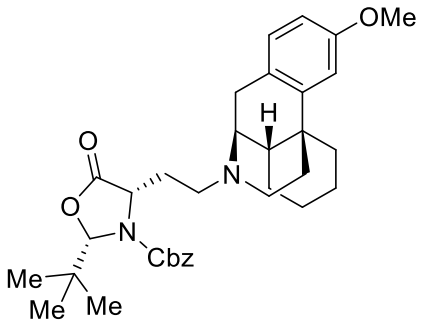
8: following the general procedure A, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (58.1 mg, 0.2 mmol, 1 equiv), 3-dimethylamino-1-propyne (65 μl, 0.6 mmol, 3 equiv), and [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (2.2 mg, 0.0020 mmol, 0.01 equiv) provided the product as a 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.



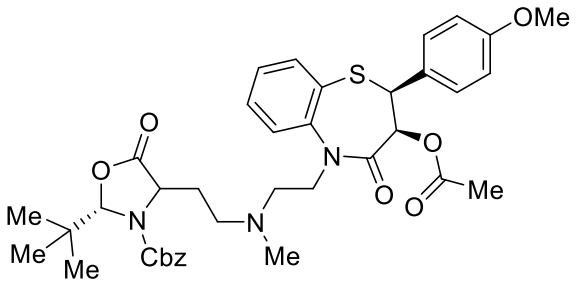
9: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (49 mg, 0.17 mmol, 1 equiv), dextromethorphan (232 mg, 0.85 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (2.4 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single 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.



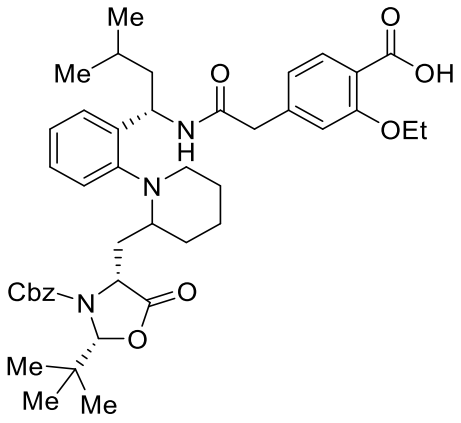
10: following the general procedure B, the reaction of benzyl 2-(tert-butyl)-4-methylene-5-oxooxazolidine-3-carboxylate (41 mg, 0.14 mmol, 1 equiv), diltiazem (293 mg, 0.71 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (1.7 mg, 0.0020 mmol, 0.01 equiv) provided the product as a single diastereomer (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:

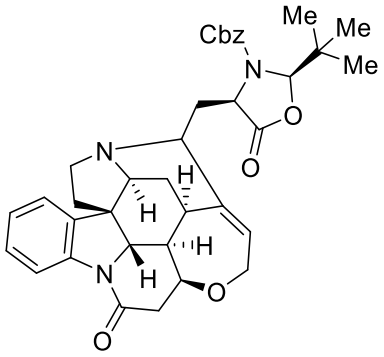
^{1}H NMR (600 MHz, $CDCl_3$) δ 10.96 (s, $1H_{dr1}$ + $1H_{dr2}$), **8.13 (d, *J* = 8.0 Hz, $1H_{dr1}$), 8.10 (d, *J* = 8.0 Hz, $1H_{dr2}$)**, 7.46 – 7.34 (m, $5H_{dr1}$ + $5H_{dr2}$), 7.25 – 6.59 (m, $6H_{dr1}$ + $6H_{dr2}$), 5.52 – 5.35 (m, $2H_{dr1}$ + $2H_{dr2}$), 5.25 – 5.09 (m, $2H_{dr1}$ + $2H_{dr2}$), 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.)

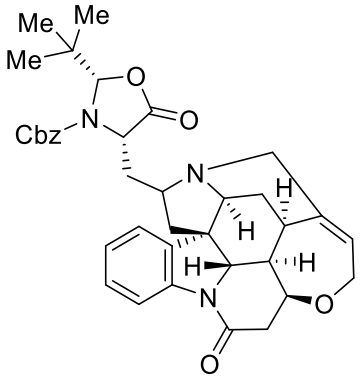
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.27 – 7.24 (m, 1H), 7.20 (d, J = 7.2 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 5.92 (s, 1H), 5.51 (s, 1H), 5.23 (s, 1H), 5.06 (s,

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).

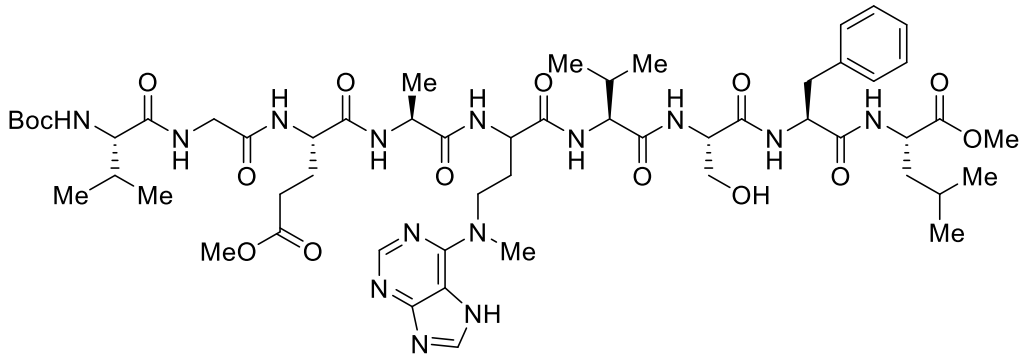
Mp: 176 °C (decomp.)

^{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).

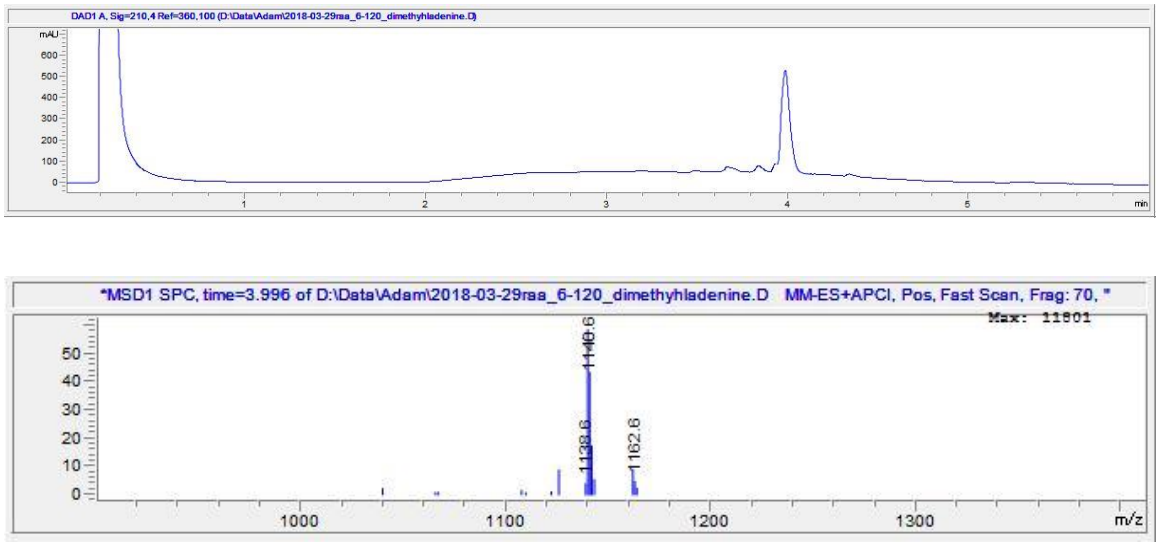
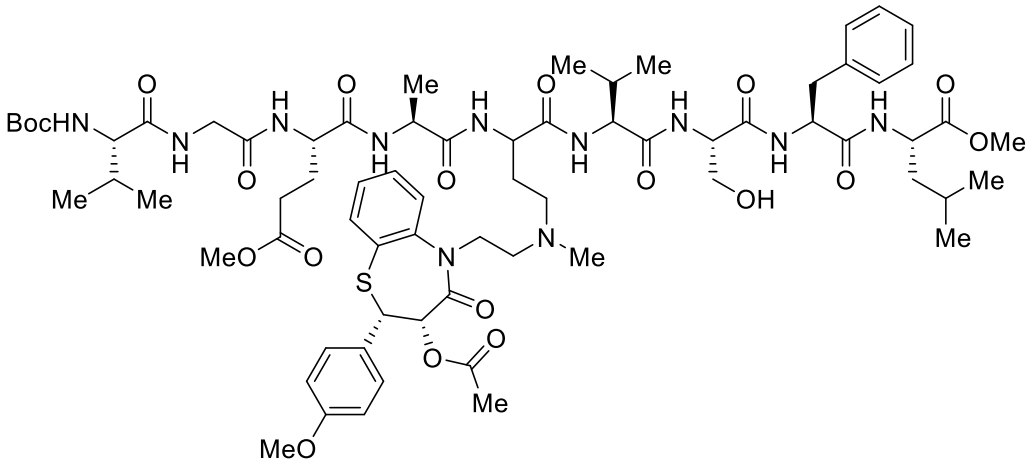


Figure S4.1. LCMS data for purified peptide **14**.



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.

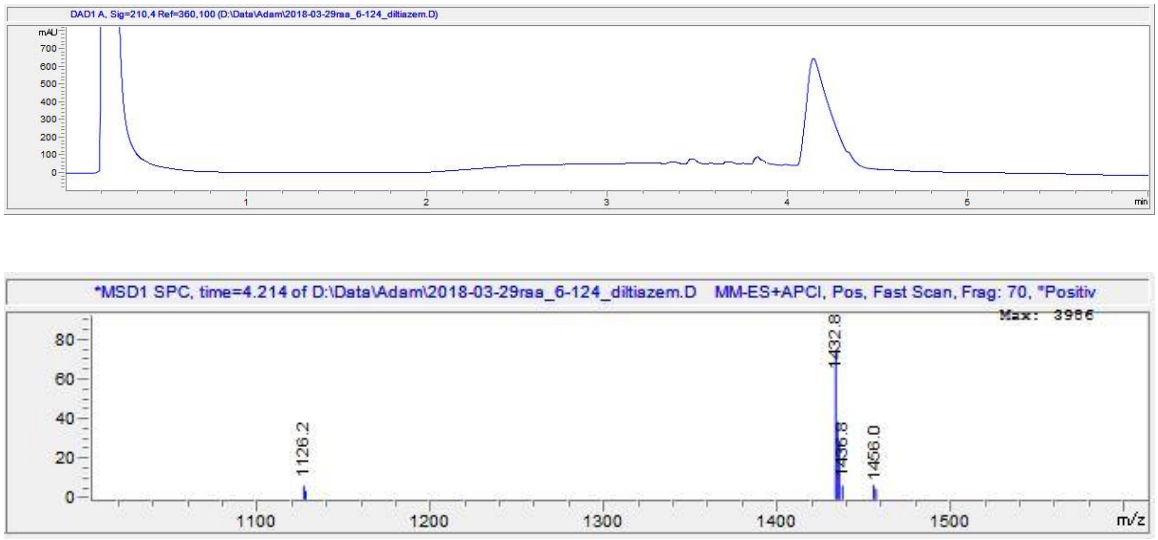
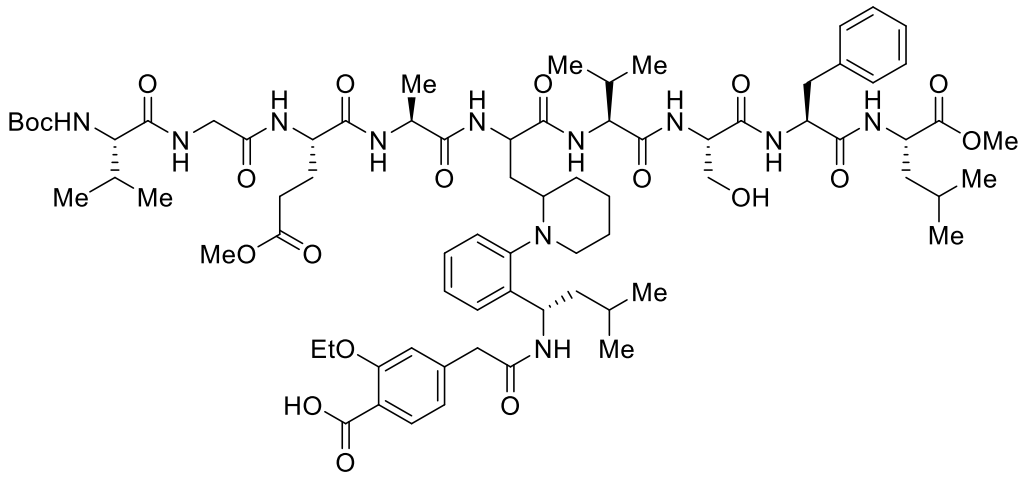


Figure S4.2. LCMS data for purified peptide **15**.



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).

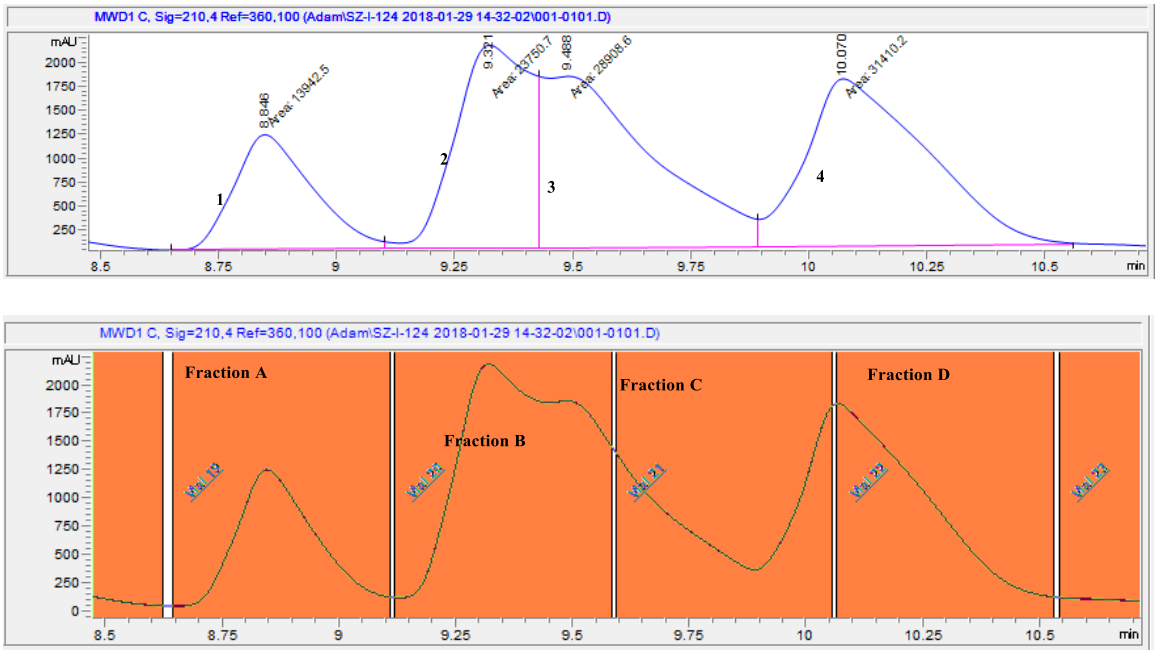


Figure S4.3. LCMS data for crude peptide **16**.

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.

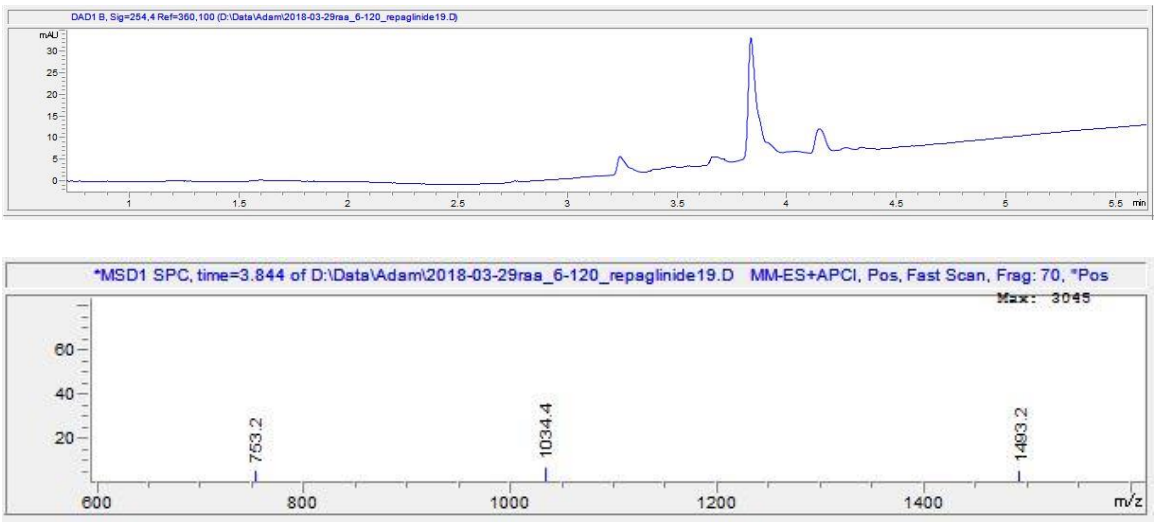


Figure S4.4. LCMS data for purified peptide **16** diastereomer 1.

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.

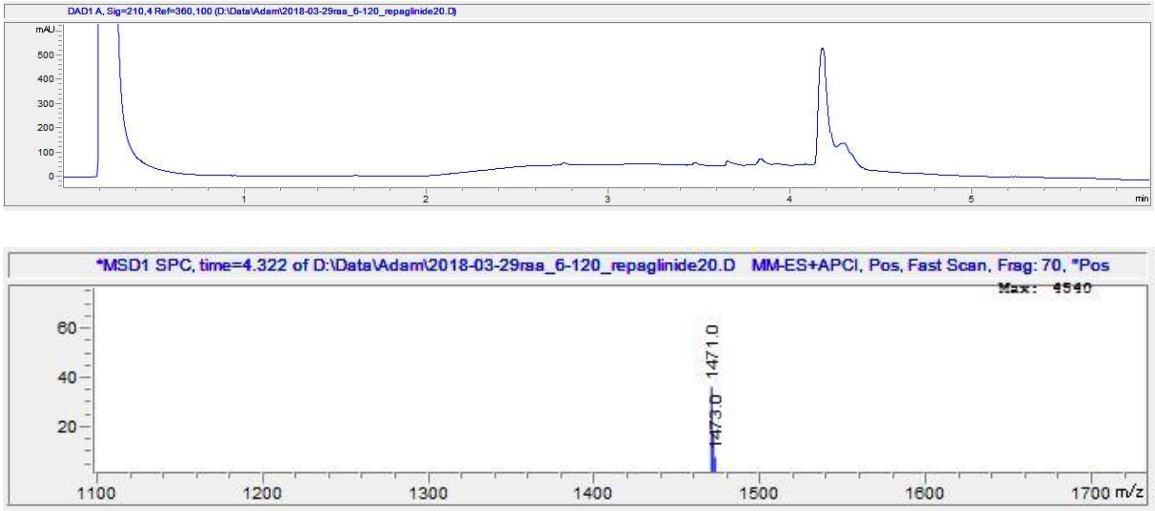


Figure S4.5. LCMS data for crude peptide **16** diastereomer 2 and 3.

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.

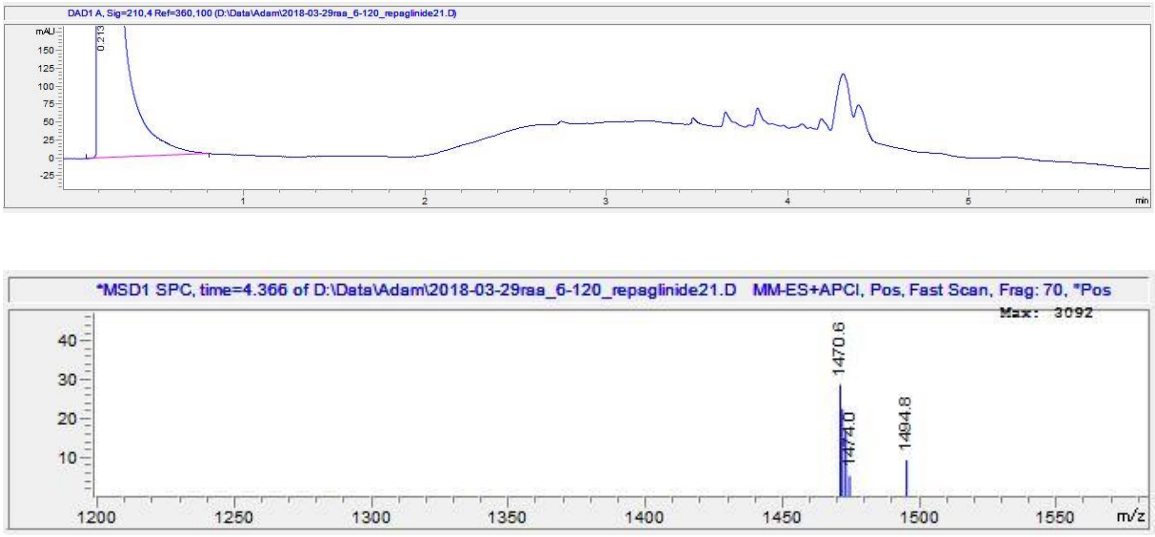


Figure S4.6. LCMS data for crude peptide **16** diastereomer 2, 3, and 4.

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.

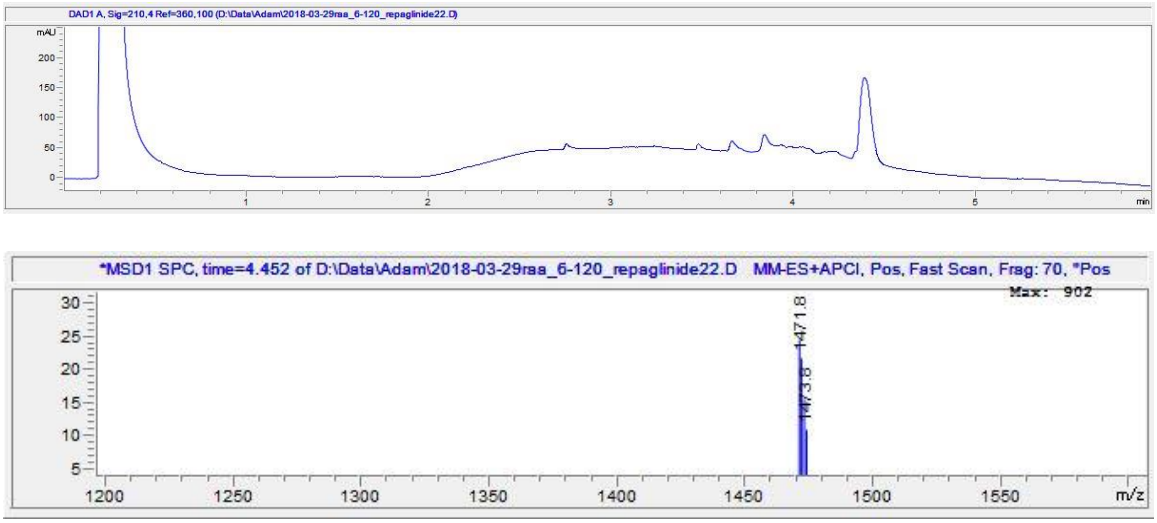
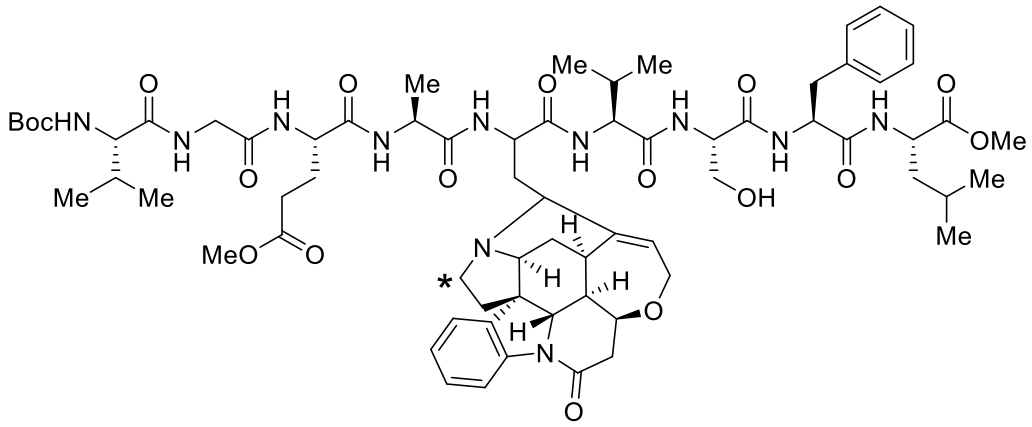


Figure S4.7. LCMS data for purified peptide **16** diastereomer 4.



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.

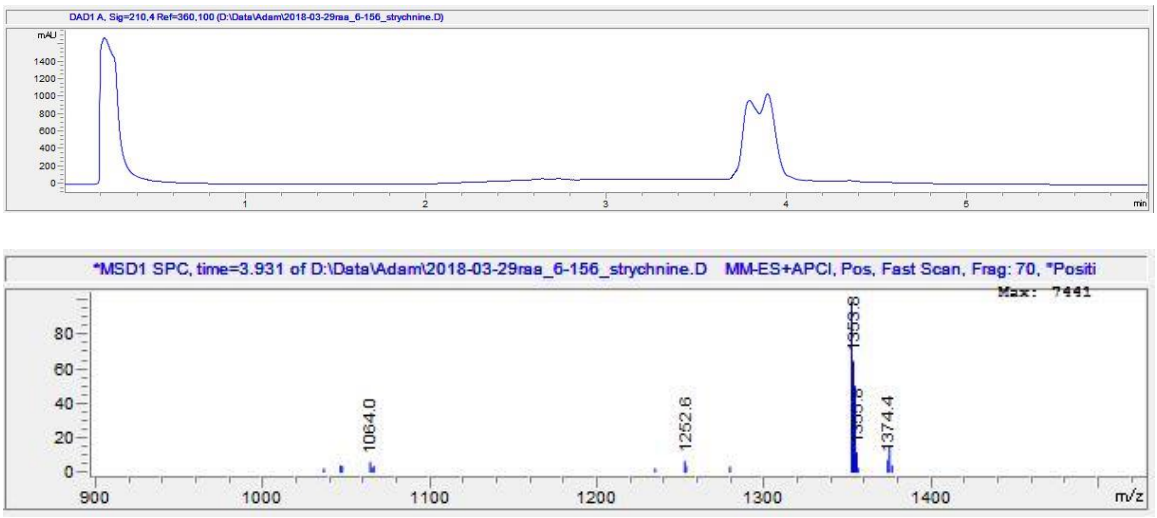
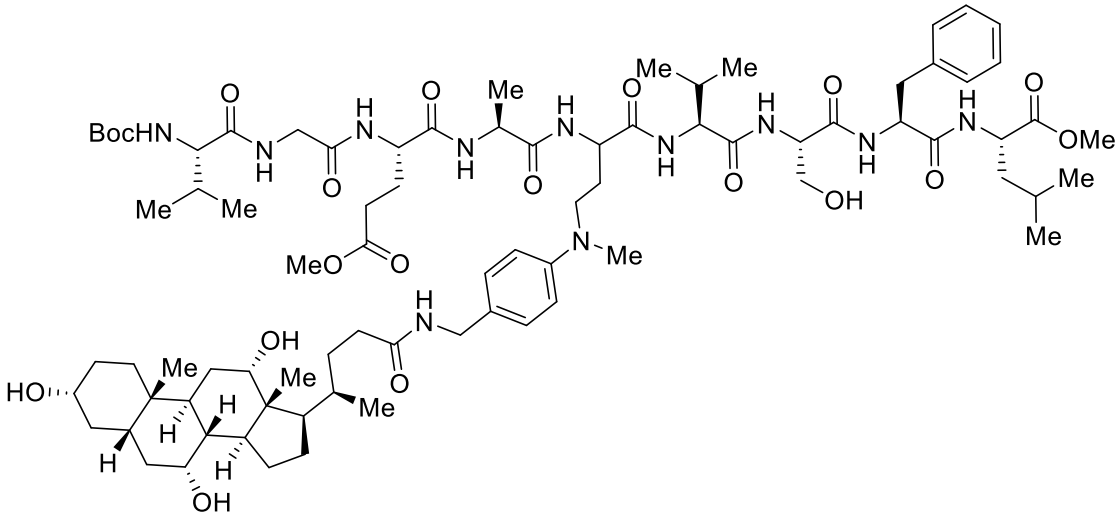


Figure S4.8. LCMS data for purified peptide **17**.



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.

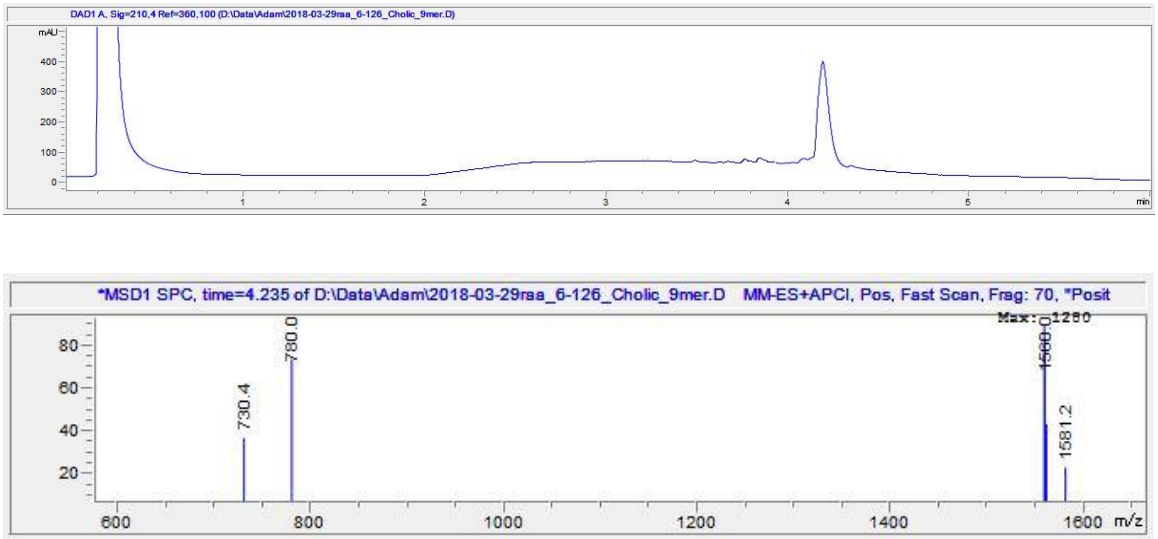
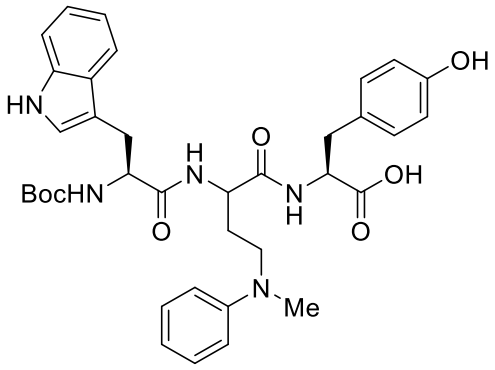


Figure S4.9. LCMS data for purified peptide **18**.



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.

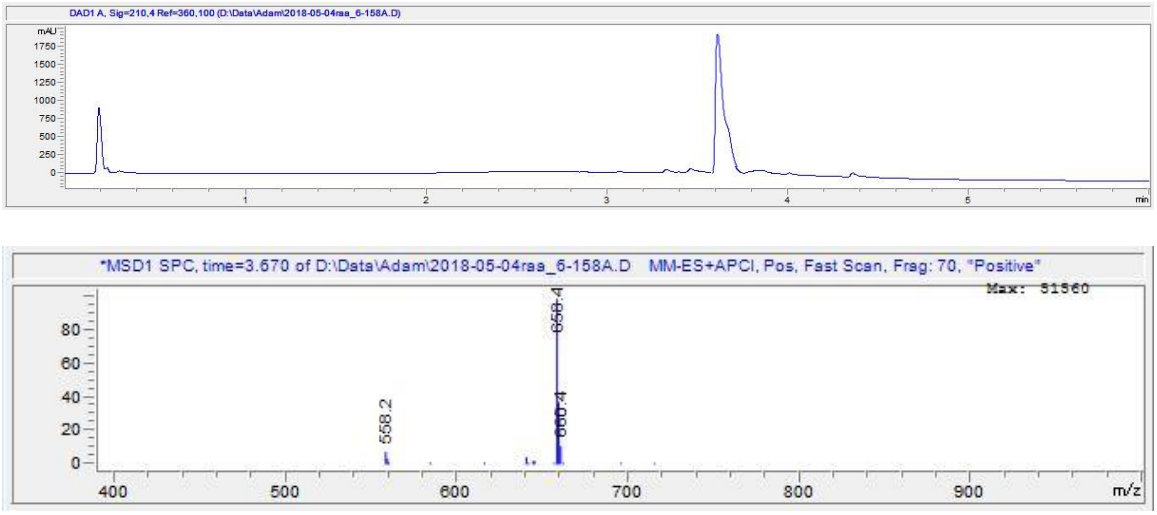
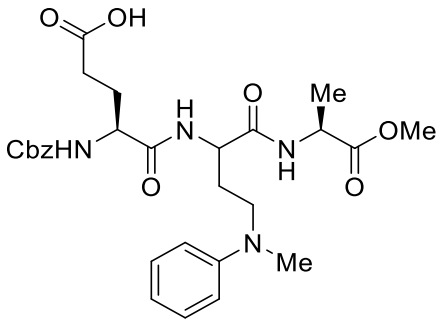


Figure S4.10. LCMS data for purified peptide **19**.



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.

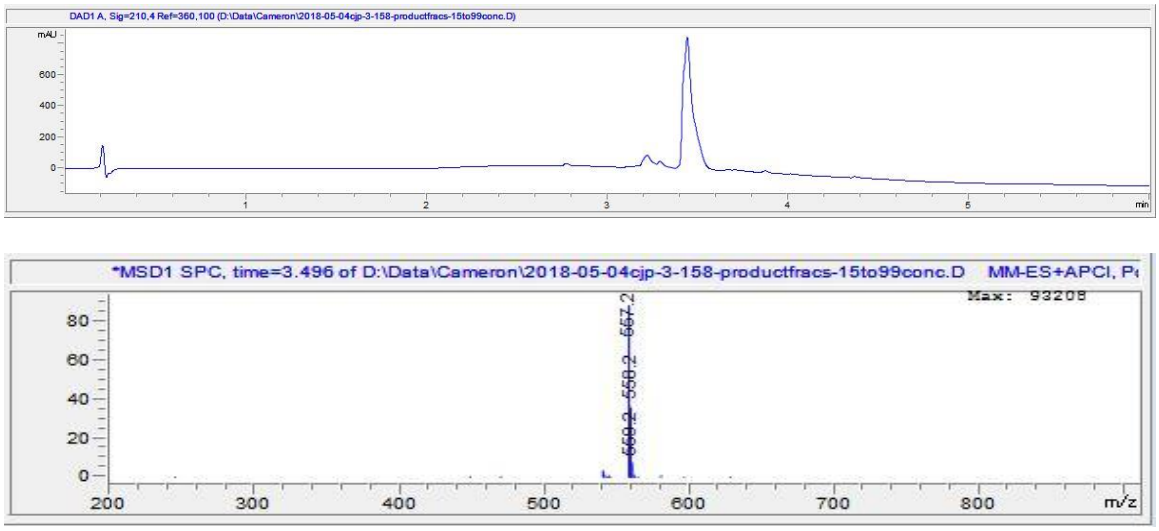
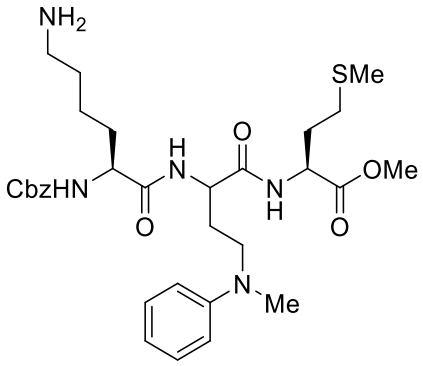


Figure S4.11. LCMS data for purified peptide **20**.



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.

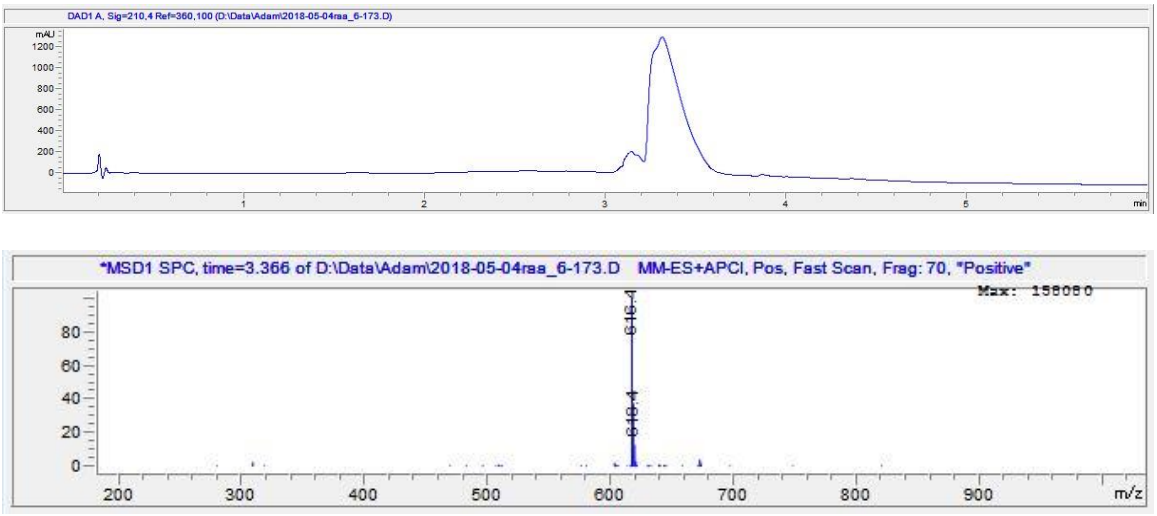
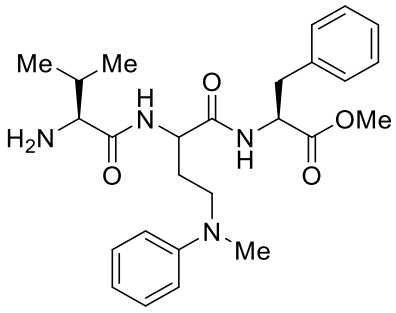


Figure S4.12. LCMS data for purified peptide **21**.



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.

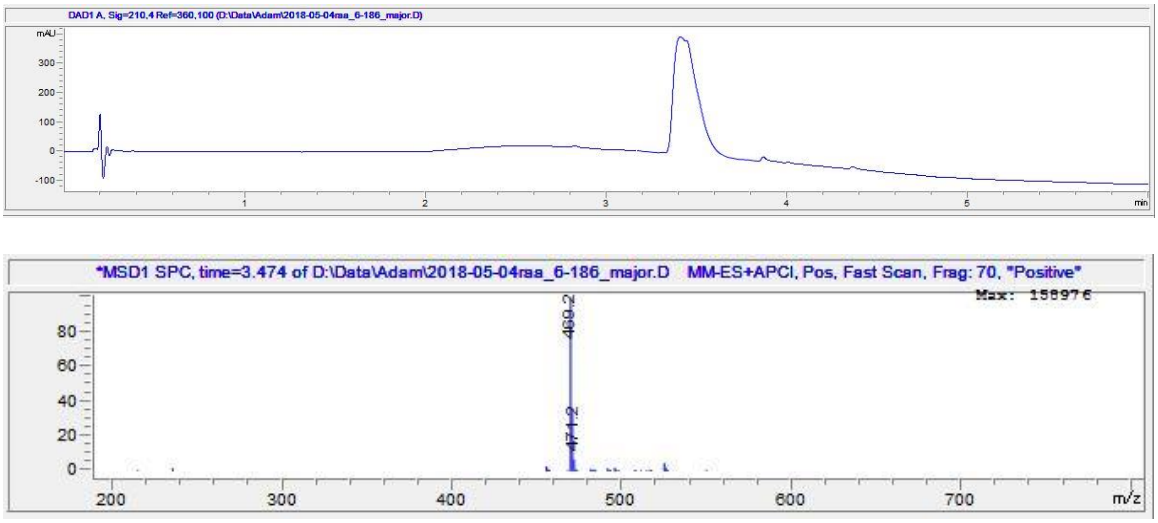


Figure S4.13. LCMS data for purified peptide **22** major diastereomer.

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.

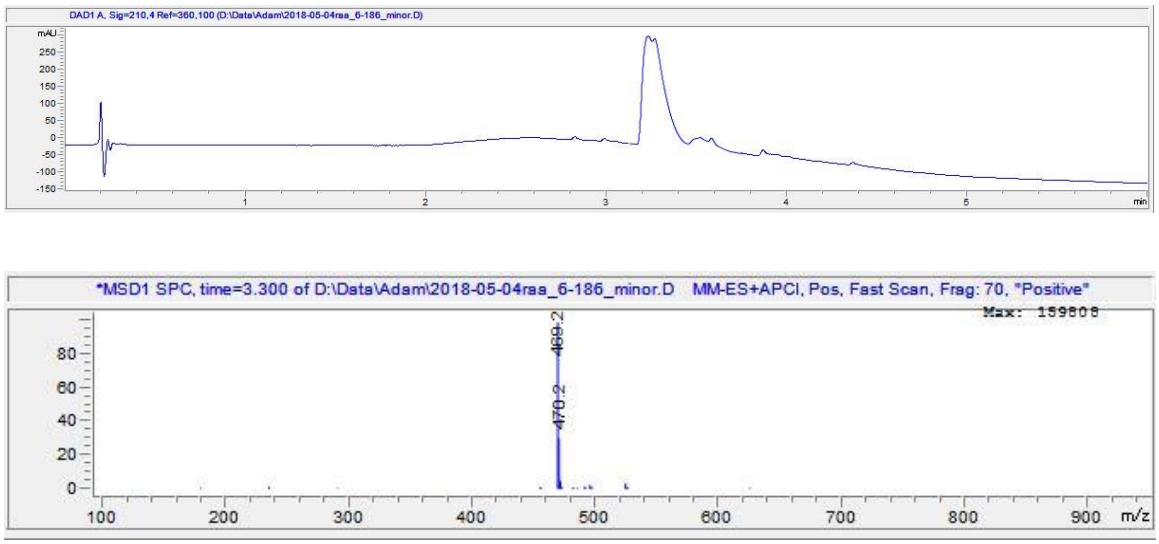
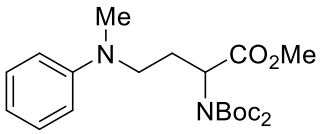


Figure S4.14. LCMS data for purified peptide **22** minor diastereomer.

4.5.7 Deprotection Procedure and Characterization Data



Methyl 2-(di(tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate: A screw-top test tube equipped with a sti9r 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

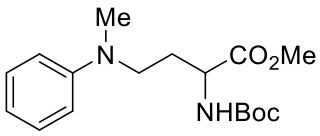
under irradiation with blue LEDs for 12 hours. The residue was purified by flash column chromatography (5 – 15% EtOAc/Hexanes) to afford the product (100 mg, 79%) as a white solid.

^{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.



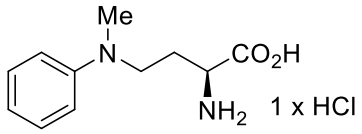
Methyl 2-((tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate: To a stirring soloution of methyl 2-(di(tert-butoxycarbonyl)amino)-4-(methyl(phenyl)amino)butanoate (13 mg, 0.03 mmol, 1 equiv) in dichloromethane (9.8 mL) was added trifluoroacetic acid (0.2 mL) dropwise. The reaction was stirred 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.



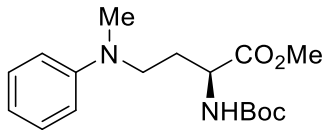
(*S*)-2-amino-4-(methyl(phenyl)amino)butanoic acid hydrochloride: To a round bottom flask equipped with a stir bar was added (+)/(-)benzyl-2-(tert-butyl)-4-(2-(methyl(phenyl)amino)ethyl)-5-oxooxazolidine-3-carboxylate (75.8 mg, 0.19 mmol, 1 equiv) and concentrated aqueous HCl (2 mL). The reaction was 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, 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.

Chapter 5

Radical α-C–H Cyclobutylation of Aniline Derivities

Adapted from: C. J. Pratt, R. A. Aycock, M. D. King, and N. T. Jui Radical α-C–H Cyclobutylation of Aniline Derivities. *Synlett.* **2019**, 31,51–54.

C. J. Pratt prepared products 3–8 and 14. M. D. King prepared starting materials.

5.1 Abstract

A catalytic system has been developed for the direct alkylation of α-C–H bonds of aniline derivatives with strained C–C σ-bonds. This method operates through a photoredox mechanism in which oxidative formation of aminoalkyl radical intermediates enables addition to a bicyclobutane derivative, giving rise to α-cyclobutyl N-alkylanilineproducts. This mild system proceeds through a redox- and proton-neutral mechanism and is operational for a range of substituted arylaminederivatives.

5.2 Introduction

The high stability of C–C single bonds typically renders them chemically inert; however, conformationally strained-ring systems display unique reactivity profiles. Early work by Wiberg and co-workers and by Gaoni demonstrated that a range of strained polycyclic hydrocarbons (some of which are shown in Figure 1) can be accessed synthetically,[1] and that they can serve as effective alkylating agents.[2,3] Indeed, because installation of cyclobutyl groups (cyclobutylation) can be accomplished through direct addition to bicyclo[1.1.0]butane (BCB) derivatives, this represents a potentially valuable method for the synthesis of cyclobutane-containing natural products or drug candidates. In addition to anionic nucleophiles,[4] organometallics,[5] and

[1] (a) Wiberg, K. B.; Ciula, R. P. Ethyl Bicyclo[1.1.0]Butane-1-Carboxylate. *J. Am. Chem. Soc.* **1959**, *81*, 5261–5262. (b) Gaoni, Y. A Simple One-Pot Preparation of 1-Arylsulfonylbicyclobutanes From Gamma,Delta-Epoxysulfones. *Tetrahedron Lett.* **1981**, *22* (43), 4339–4340. (c) Wiberg, K. B.; Walker, F. H. [1.1.1]Propellane. *J. Am. Chem. Soc.* **1982**, *104* (19), 5239–5240.

[2] Gaoni, Y.; Tomazic, A. Bridgehead Reactivity, Nucleophilic and Radical Additions, and Lithium Aluminum Hydride Reduction of 1-(Arylsulfonyl)Bicyclobutanes: General Access to Substituted, Functionalized Cyclobutanes. Syntheses of Citrilol Acetate, Junione, and the Tricyclo[3.3.0.0]Octane and Tricyclo[4.3.0.0]Nonane Ring Systems. *J. Chem. Soc., Chem. Commun* **1985**, *50* (2), 40–43.

[3] Wiberg, K. B. Small-Ring Propellanes. *Chem. Rev* **1989**, *89*, 975–983.

[4] (a) Blanchard Jr., E. P.; Cairncross, A. Bicyclo[1.1.0]Butane Chemistry. I. The Synthesis and Reactions of 3-Methylbicyclo[1.1.0]Butanecarbonitriles. *J. Am. Chem. Soc.* **1966**, *88*, 487–495. (b) Hall Jr., H. K.; Blanchard Jr., E. P.; Cherkofsky, S. C.; Sieja, J. B.; Sheppard, W. A. Synthesis and Polymerization of 1-Bicyclobutanecarbonitriles. *J. Am. Chem. Soc.* **1971**, *93*, 110–120. (c) Gaoni, Y. New Bridgehead-Substituted 1-(Arylsulfonyl)Bicyclo[1.1.0]Butanes and Some Novel Addition Reactions of the Bicyclic System. **1989**, *45* (9), 2819–2840.

[5] (a) Gaoni, Y.; Tomazic, A. Bridgehead Reactivity, Nucleophilic and Radical Additions, and Lithium Aluminum Hydride Reduction of 1-(Arylsulfonyl)Bicyclobutanes: General Access to Substituted, Functionalized Cyclobutanes. Syntheses of Citrilol Acetate, Junione, and the Tricyclo[3.3.0.0]Octane and Tricyclo[4.3.0.0]Nonane Ring Systems. *J. Chem. Soc., Chem. Commun*

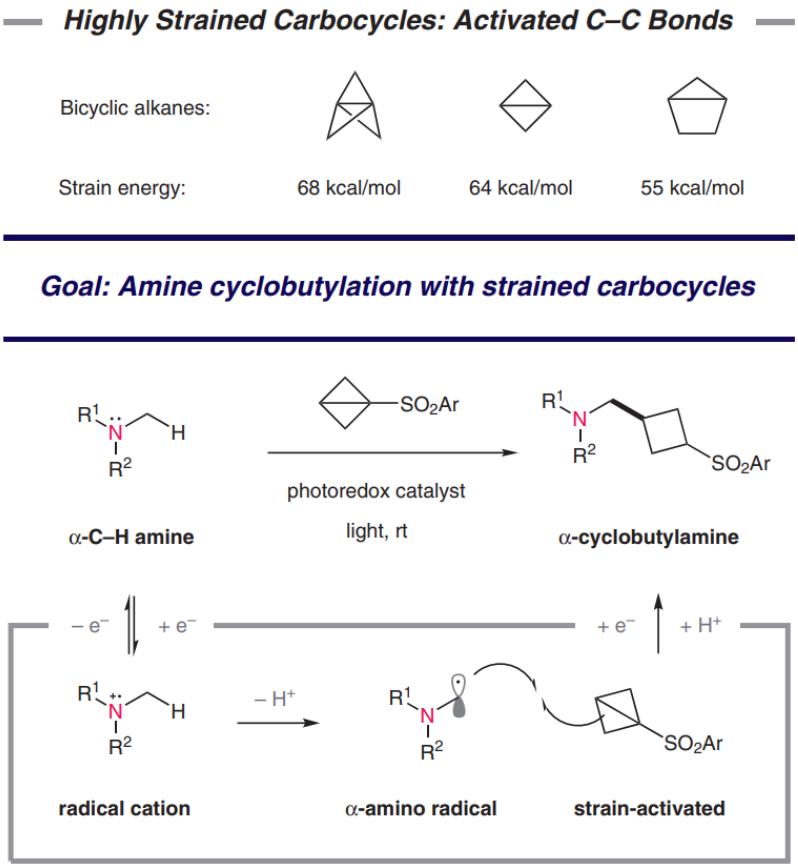


Figure 5.1. Strategy for cyclobutylation through addition to strained bicyclic alkanes. The strain energy for each molecule is derived by comparing δH_f with a hypothetical strainless model, as discussed by Wiberg.[6]

1985, *50* (2), 40–43. (b) Panish, R.; Chintala, S. R.; Boruta, D. T.; Fang, Y.; Taylor, M. T.; Fox, J. M. Enantioselective Synthesis of Cyclobutanes via Sequential Rh-Catalyzed Bicyclobutanation/Cu-Catalyzed Homoconjugate Addition. *J. Am. Chem. Soc.* **2013**, *135* (25), 9283–9286. (c) Fawcett, A.; Biberger, T.; Aggarwal, V. K. Carbopalladation of C–C σ-Bonds Enabled by Strained Boronate Complexes. *Nat. Chem.* **2019**, *11* (2), 117–122.

[6] .

amines,[7,8] strained BCBs are effective coupling partners for radical species.[4b,9] Over the past few years, our laboratory has been interested in developing new methods that permit selective reactions through the use of photoredox catalysis. As part of this program, we recently developed a system for the direct addition of nonactivated amines to peptides through the formation of the corresponding α -amino radicals.[10] This process is highly selective and it functions through a redox- and proton-neutral mechanism, such that stoichiometric additives are not required. We questioned whether these aminoalkyl radical intermediates[11] could be intercepted by strain-activated BCB derivatives in a direct cyclobutylation reaction with amines. Although a number of impressive methods for cyclobutylation of radical intermediates have been described, most recently by the groups of Lin[12] and Aggarwal,[13] this approach (outlined in Figure 1) would be unique, in part because it would potentially function on a range of nonactivated amine-containing substrates, without the need for programmed radical formation (i.e., halogen installation, etc.). We considered the catalytic pathway shown in Figure 1, in which photoinduced electron transfer from the amine substrate to a photoredox catalyst would give rise to a radical cation. Deprotonation of the newly acidified C–H bond would afford a key α -amino radical species.[14] Attack of this

[7] Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Amination. *Science*. **2016**, *351* (6270).

[8] Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C. M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139* (8), 3209–3226.

[9] Wiberg, K. B.; Lampman, G. M.; Ciula, R P; Connor, D. S.; Schertler, P.; Lavanish, J. Bicyclo[1.1.0]Butane. *Tetrahedron* **1965**, *21*, 2749–2769.

[10] Aycock, R. A.; Pratt, C. J.; Jui, N. T. Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides. *ACS Catal.* **2018**, *8* (10), 9115–9119.

[11] Mcnally, A.; Prier, C. K.; Macmillan, D. W. C. Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science (80-.).* **2011**, *334* (November), 1114–1117.

[12] Wu, X.; Hao, W.; Ye, K. Y.; Jiang, B.; Pombar, G.; Song, Z.; Lin, S. Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors. *J. Am. Chem. Soc.* **2018**, *140* (44), 14836–14843.

[13] Silvi, M.; Aggarwal, V. K. Radical Addition to Strained σ-Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters. *J. Am. Chem. Soc.* **2019**, *141* (24), 9511–9515.

[14] (a) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. Visible Light Photoredox Catalysis: Generation and Addition of N -Aryltetrahydroisoquinoline-Derived α-Amino Radicals to Michael Acceptors. *Org. Lett.* **2012**, *14* (3), 672–675. (b) Wiberg, K. B. The Concept of Strain in Organic Chemistry. *Angew. Chemie Int. Ed. English* **1986**, *25* (4), 312–322. (c)Yoon, U.-C.; Kim, J.-U. Electron-Transfer Photochemistry of Alpha-Silylamine-Cyclohexenone Systems. Medium Effects on Reaction Pathways Followed. *J. Am. Chem. Soc.* **1987**, *109*, 4421–4423. (d) Ruiz Espelt, L.; Wiensch, E. M.; Yoon, T. P. Brønsted Acid Cocatalysts in

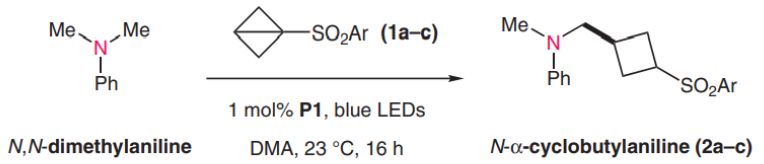
intermediate species on a strain-activated bicyclo[1.1.0]butane would afford a new C–C bond, and single electron reduction and protonation would deliver the desired -cyclobutylamine This system would operate in a redox- and proton-neutral manner, without the need for exogenous chemical additives

5.3 Results and discussion

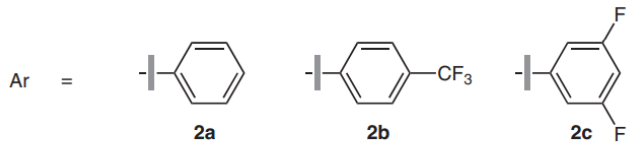
To evaluate the feasibility of this proposed transformation, we treated N,N-dimethylaniline with a small series of BCB reagents 1a–c to afford the corresponding cyclobutylated products 2a–c (Table 5.1). In the presence of 1 mol% of Ir[dF(CF3)ppy]2(dtbbpy)·PF_6 [P1; dF = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4′-di-tert-butyl-2,2′-bipyridine] and blue light in N,N-dimethylacetamide (DMA), phenylsulfone 1a gave the desired product 2a in a promising yield (28%, as determined by NMR with an internal standard). Increasing the electron-withdrawing capacity of the sulfonyl activating group resulted in improved reactivity with aminoalkyl radicals. Specifically, the fluorinated phenylsulfone derivatives 1b and 1c gave the corresponding cyclobutane products 2b and 2c in yields of 64 and 69%, respectively. In this system, the aniline substrate was used as the excess reagent (five equivalents with respect to the BCB reagent) to suppress further activation and cyclobutylation of the desired products 2. Importantly, this process was not operational in the absence of a photoredox catalyst or light

Photocatalytic Radical Addition of α-Amino C-H Bonds across Michael Acceptors. *J. Org. Chem.* **2013**, *78* (8), 4107–4114. (e)Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. Enantioselective Conjugate Additions of α-Amino Radicals via Cooperative Photoredox and Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2015**, *137* (7), 2452–2455. (f) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. Asymmetric Catalytic Formation of Quaternary Carbons by Iminium Ion Trapping of Radicals. *Nature* **2016**, *532* (7598), 218–222. (g) Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. Photoredox Catalysis in a Complex Pharmaceutical Setting: Toward the Preparation of JAK2 Inhibitor LY2784544. *J. Org. Chem.* **2014**, *79* (23), 11631–11643. (h) Trowbridge, A.; Reich, D.; Gaunt, M. J. Multicomponent Synthesis of Tertiary Alkylamines by Photocatalytic Olefin-Hydroaminoalkylation. *Nature* **2018**, *561* (7724), 522–527. (i) Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined Synthesis of C(Sp3)-Rich N-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141* (21), 8426–8430. (j) Wu, Y.; Hu, L.; Li, Z.; Deng, L. Catalytic Asymmetric Umpolung Reactions of Imines. *Nature* **2015**, *523* (7561), 445–450

Table 5.1 Optimal Conditions for α-Cyclobutylation of N,N-Dimethylaniline



N,N-dimethylaniline — *N*-α-cyclobutylaniline (2a–c)



2a 2b 2c

***yield of 2*:** 28% (from **1a**) 64% (from **1b**) 69% (from **1c**)

Entry	Deviation from above conditions (with **1c**)	Yield (%) of **2c**
1	Reaction without catalyst	0
2	Reaction without blue light	0
3	1 mol% $Ir[(ppy)_2(dtbbpy)]\cdot PF_6$[a] (**P2**) as catalyst	35
4	5 mol% 5CzBn[b] (**P3**) as catalyst	64
5	MeCN as solvent	48
6	DCE as solvent	46
7	DMSO as solvent	51

[a] ppy = 2-phenylpyridine.

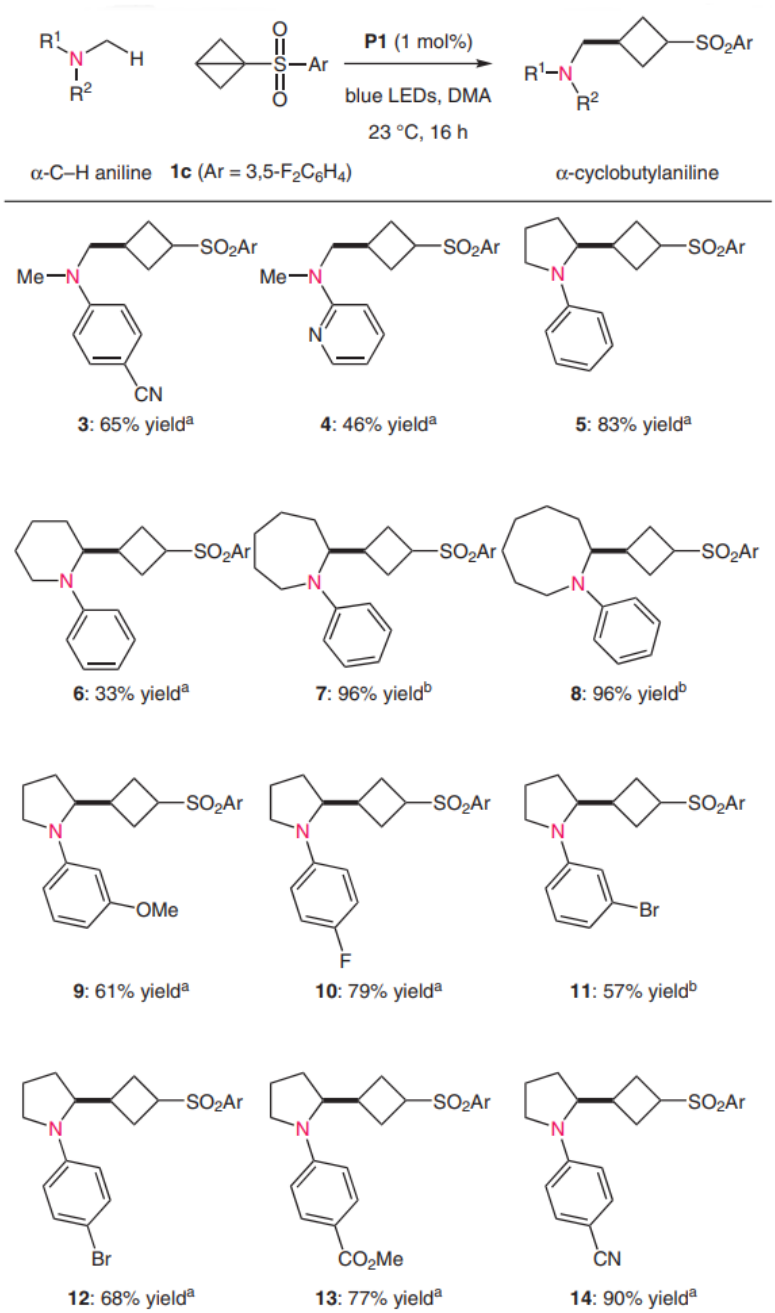
(Table 5.1, entries 1 and 2; 0% yield). Other catalysts could also be employed to accomplish this transformation, although less-oxidizing iridium catalysts (such as P2; entry 3: 35% yield) or organic dyes [including penta9H-carbazol-9-ylbenzonitrile (5CzBn; P3) (entry 4: 64% yield)] were less efficient across an array of substrates. A variety of aprotic organic solvents could be utilized here with acceptable levels of reaction efficiency (entries 5–7; 46– 51% yield). Having identified an effective protocol for the α -alkylation of anilines with BCB 1c, we evaluated the substrate scope of this process (again utilizing 1c as the limiting reagent with five equivalents of

the aniline substrate).[15] As shown in Table 5.2, electron-deficient dimethylaniline derivatives reacted under standard conditions to give the corresponding products 3 and 4 in yields of 65 and 46%, respectively. Cyclic aniline derivatives were also effectively transformed into the corresponding cyclobutylated products. For example, N-phenylpyrrolidine reacted well to afford 5 in 83% isolated yield. These conditions were less effective for the coupling of N-phenylpiperidine (which gave 6 in 33% yield, with 55% remaining starting material), presumably due to increased steric constraints. However, seven- and eight-membered saturated nitrogen heterocycles were excellent substrates, giving rise to the corresponding cyclobutanes 7 and 8 in near-quantitative yield (96% in each case).[16] In accord with earlier reports,[21] aniline derivatives with electron-donating groups in the ortho- or para-positions were not reactive in this system, where coupling attempts uniformly returned the starting materials. However, these conditions were effective for the transformation of electron-deficient aniline derivatives. Alkylation of a variety of N-arylpyrrolidines occurred smoothly; a methoxy substituent was well tolerated in the meta-position (9; 61% yield), as were fluoro and bromo substituents (10–12; 57–79% yield). As expected, the methoxycarbonyl- and nitrile-substituted phenylpyrrolidines were excellent substrates for this transformation, giving rise to products 13 and 14 in yields of 77 and 90%, respectively. In most cases, the products were isolated as roughly equal (<2:1) mixtures of cis- and

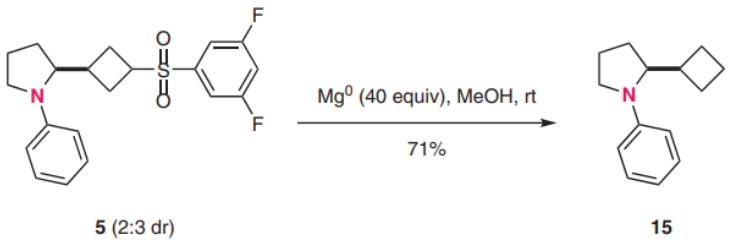
[15] A screw-top test tube equipped with a stirrer bar was charged with [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]·PF_6 (1 mol%), 1C (1 equiv), and, if solid, the appropriate aniline (5 equiv). The tube was sealed with a PTFE/silicon septum and connected to a Schlenck line. The atmosphere was exchanged by applying a vacuum and backfilling with N_2 (this process was conducted a total of three times). Under a N2 atmosphere, the tube was charged by syringe with previously degassed solvent (DMA; 2 mL/mmol 1C) and, if liquid, the appropriate aniline. The resulting solution was stirred at 700 rpm and irradiated with blue LEDs (4 cm from the lamp) for 16 h. The reaction was then quenched with sat. aq $NaHCO_3$ (10 mL), and the mixture was extracted with EtOAc (3 × 15 mL). The combined extracts were washed sequentially with 5% aq LiCl (3 × 15 mL) and brine (2 × 15 mL), dried (Na_2SO4), and concentrated in vacuo. The residue was purified by chromatography (silica gel) to give the desired product. See the Supporting Information for full details, along with physical and spectroscopic data for the products.

trans-cyclobutane stereoisomers. Slightly higher selectivity was observed in a few cases (7, 8, and 11: ~2.3:1 ratio); although chromatographic separation of these

Table 5.2. Scope of Anilines. [a] < 2:1 dr, [b] 2.3:1 dr.



diastereomers was often difficult, we were able to purify the major isomer of 7. Crystallization of this isomer permitted its analysis by X-ray crystallography, which demonstrated that the major isomer in this case was the cis-cyclobutane, consistent with protonation occurring from the less sterically hindered face of the cyclobutene ring. The synthetic utility of arylsulfonylcyclobutanes has been extensively demonstrated by the Baran group.[13] In line with these reports, reductive desulfonylation of product 5 occurred smoothly in the presence of excess magnesium in methanol at room temperature to give 71% yield of the cyclobutyl product 15, as shown in Scheme 5.1.



Scheme 5.1 Reductive desulfonation of arylsulfonylcyclobutane 5

5.4 Conclusion

In summary, we have developed a mild system for the direct C–H cyclobutylation of aniline derivates. This process operates through formation of an α -amino radical, followed by direct addition to a strained BCB derivative. The disclosed protocol readily functionalizes a range of N-aryl amines and heterocyclic compounds of various ring sizes. In accord with previous reports, electron-deficient aniline derivates were shown to be efficient coupling partners. Because the resulting sulfonyl cyclobutane products have been shown to capable of being manipulated in a

number of ways, we anticipate this process will be an attractive method for the generation of a range of α-cyclobutyl amine derivatives

5.5 Experimental Information

5.5.1 General Information

General Reagent 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, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$,[17] $[Ir(ppy)_2(dtbbpy)]PF_6$,[18] 5CzBN,[19] 4CzIPN,[18] and 3DPAFIPN[18] were prepared according to literature procedures. 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.

General Analytical Information:

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

[17] Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S.; Rohl, R. Article Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium (III) Complex Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium (III) Complex. *Society* **2005**, No. III, 5712–5719.

[18] Lowry, M. S.; Hudson, W. R.; Pascal, R. A.; Bernhard, S. Accelerated Luminophore Discovery through Combinatorial Synthesis. *J. Am. Chem. Soc.* **2004**, *126* (43), 14129–14135.

[19] Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor−Acceptor Cyanoarenes. *J. Am. Chem. Soc* **2018**, *140*, 15353–15365.

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 ^1H NMR and 77.23 ppm for ^{13}C NMR). Adduct yields for comparison of bicyclobutane (BCB) reagents (**1a-1c**) were obtained via ^1H 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.

5.5.2 General Procedures:

Procedure for Radical Conjugate Addition

A screw-top test tube equipped with a stir bar was charged with $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]$ 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 solution 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) and brine (2 x 15 ml), dried with Na_2SO_4, concentrated in vacuo, and purified by silica gel chromatography 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 eqiv). 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, concentrated in vacuo, and purified by silica gel chromatography to afford the title compound.

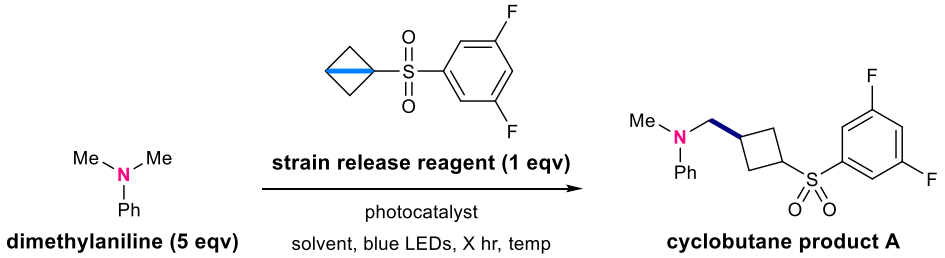
5.5.3 Optimization Details

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 of the mixture was analyzed by ^{19}F NMR, and the integral values were used to calculate yield.

Optimization Table:

Table S5.1. The influence of solvent, catalyst, temperature, and time on yield of cyclobutane product A.



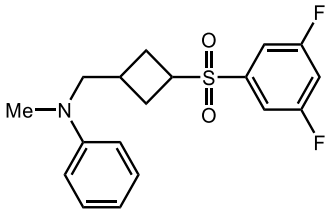
Catalyst	Solvent	Temperature	Time	% Yield A[1]
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMF	23 °C	16 hr	63%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DCM	23 °C	16 hr	27%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	Toluene	23 °C	16 hr	42%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DCE	23 °C	16 hr	46%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	MeCN	23 °C	16 hr	48%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMSO	23 °C	16 hr	51%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	23 °C	16 hr	69%
$[Ir(dtbbpy)(ppy)_2]PF_6$	DMA	23 °C	16 hr	35%
5CzBn (5%)	DMA	23 °C	16 hr	64%
4CzIPN	DMA	23 °C	16 hr	56%
3DPAFIPN	DMA	23 °C	16 hr	26%
EOSIN Y	DMA	23 °C	16 hr	14%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	50 °C	16 hr	57%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	80 °C	16 hr	53%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	23 °C	24 hr	67%
none	DMA	23 °C	16 hr	0%
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	DMA	23 °C	16 hr	0%[2]

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

5.5.4 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.[20]

5.5.5 Procedure and Characterization Data



***N*-((3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)methyl)-*N*-methylaniline, 2c:**

Following 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 $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.8 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture 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).

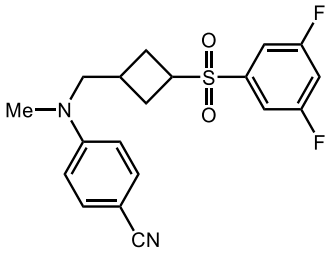
[20] (a) Xu, G. Q.; Feng, Z. T.; Xu, J. T.; Wang, Z. Y.; Qin, Y.; Xu, P. F. Transition-Metal-Free Selective C−H Benzylation of Tertiary Arylamines by a Dearomatization-Aromatization Sequence. *Chem. - A Eur. J.* **2018**, *24* (52), 13778–13782. (b) Zhou, W.; Fan, M.; Yin, J.; Jiang, Y.; Ma, D. CuI/Oxalic Diamide Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides and Amines. *J. Am. Chem. Soc.* **2015**, *137* (37), 11942–11945. (c) Fukino, N.; Kamino, S.; Takahashi, M.; Sawada, D. Synthesis of Aminobenzopyranoxanthenes with Nitrogen-Containing Fused Rings. *J. Org. Chem.* **2017**, *82* (24), 13626–13631. (d) Xu, G. Q.; Xu, J. T.; Feng, Z. T.; Liang, H.; Wang, Z. Y.; Qin, Y.; Xu, P. F. Dual C(Sp 3)−H Bond Functionalization of N-Heterocycles through Sequential Visible-Light Photocatalyzed Dehydrogenation/[2+2] Cycloaddition Reactions. *Angew. Chemie - Int. Ed.* **2018**, *57* (18), 5110–5114. (e) Ma, D.; Cai, Q.; Zhang, H. Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides. *Org. Lett.* **2003**, *5* (14), 2453–2455. (f) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C. M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139* (8), 3209–3226

For the mixture of diastereomers:

^{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 -104.9 (dd, *J* = 8.0, 5.6 Hz), -104.9 (dd, *J* = 8.6, 5.0 Hz.



4-(((3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)methyl)(methyl)amino)benzonitrile, 3: Following 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 $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.0 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture of diastereomers (123 mg,

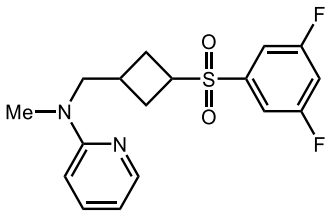
65% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear oil after purification by flash column chromatography (40% ethyl acetate:hexanes).

For the mixture of diastereomers:

^{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 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-

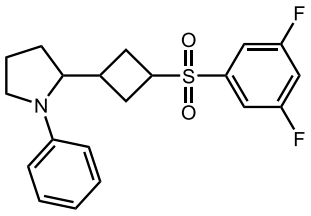
(dimethylamino)pyridine (310 µl, 2.5 mmol, 5 equiv), and [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (6.0 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixmixture of diastereomers (123 mg, 46% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear oil after purification by flash column chromatography (30% ethyl acetate:hexanes).

For the mixture of diastereomers:

^{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 general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115.6 mg, 0.5

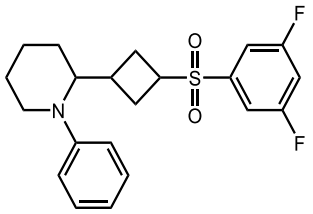
mmol, 1 equiv), 1-phenylpyrrolidine (360 µl, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.8 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture of diastereomers (157 mg, 83% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (30% ethyl acetate:hexanes).

For the mixture of diastereomers:

^{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)



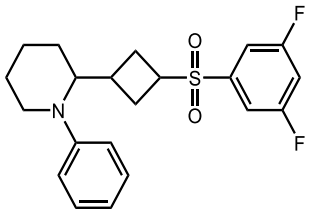
2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpiperidine, 6a: Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115.1 mg, 0.5 mmol, 1 equiv), 1-phenylpiperidine (400 µl, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.5 mg, 0.005 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 diastereomer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.26 – 7.22 (m, 2H), 7.18 – 7.12 (m, 2H), 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)



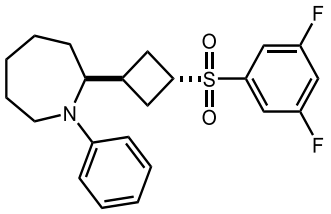
2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpiperidine, 6b: Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (114.8 mg, 0.5 mmol, 1 equiv), 1-phenylpiperidine (400 µl, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.7 mg, 0.005 mmol, 0.01 equiv) provided the product (27 mg, 14% yield) as a clear oil after purification by flash column chromatography (5% ethyl acetate:hexanes to 20% ethyl acetate:hexanes).

For the minor diastereomeromer:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 – 7.29 (m, 2H), 7.18 (t, *J* = 7.9 Hz, 2H), 7.05 (tt, *J* = 8.4, 2.3 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 3.72 (dt, *J* = 10.9, 3.8 Hz, 1H), 3.57 (tt, *J* = 9.4, 4.7 Hz, 1H), 3.30 (dd, *J* = 13.0, 3.2 Hz, 1H), 3.2 (m, 1H), 3.00 (m, 1H), 2.55 (ddt, *J* = 13.1, 8.3, 3.7 Hz, 1H), 2.20 (dq, *J* = 13.3, 4.7, 4.2 Hz, 1H), 1.99 (ddd, *J* = 16.8, 8.8, 4.9 Hz, 1H), 1.84 (dt, *J* = 13.5, 8.4 Hz, 1H), 1.67 (ddd, *J* = 15.3, 10.6, 4.8 Hz, 1H), 1.58 – 1.50 (m, 4H), 1.48 (dd, *J* = 12.8, 3.3 Hz, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.8 (d, *J* = 11.4 Hz), 162.1 (d, *J* = 11.4 Hz), 151.7, 151.7, 141.5 (t, *J* = 7.8 Hz), 129.1, 118.9, 117.2, 112.0, 111.9 (dd, *J* = 21.7, 6.4 Hz), 109.3 (t, *J* = 25.0 Hz), 61.8, 54.5, 44.0, 30.8, 27.0, 26.5, 25.0, 24.6, 19.7.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -105.06 (dt, *J* = 9.0, 4.9 Hz)

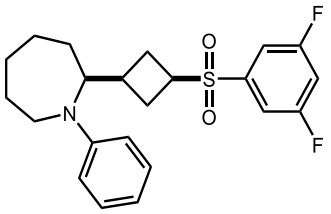


2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazepane, 7*trans*: Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116.6 mg, 0.5 mmol, 1 equiv), 1-phenylazepane (450 µl, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.4 mg, 0.005 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 = 7.40 – 7.35 (m, 2H), 7.15 (dd, J = 8.9, 7.1 Hz, 2H), 7.04 (tt, J = 8.4, 2.3 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 6.57 (t, J = 7.2 Hz, 1H), 3.84 (td, J = 9.1, 6.4 Hz, 1H), 3.69 – 3.58 (m, 2H), 3.07 (ddd, J = 15.7, 11.5, 2.0 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.66 – 2.58 (m, 1H), 2.50 – 2.42 (m, 1H), 2.24 – 2.13 (m, 2H), 2.13 – 2.04 (m, 1H), 1.74 – 1.65 (m, 3H), 1.53 – 1.51 (m, 1H), 1.37 – 1.22 (m, 2H), 1.20 – 1.13 (m, 1H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 162.9 (dd, J = 255.9, 11.4 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)

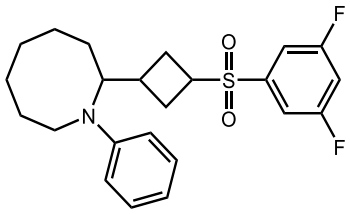


2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazepane, 7*cis*: Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116.6 mg, 0.5 mmol, 1 equiv), 1-phenylazepane (450 µl, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.4 mg, 0.005 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 162.8 (dd, J = 255.8, 11.4 Hz), 148.5, 141.3 (t, J = 7.8 Hz), 129.4, 115.1, 112.1 – 111.7 (m), 110.8, 109.4 (t, J = 24.9 Hz), 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)



2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazocane, 8: Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (116 mg, 0.5 mmol, 1 equiv), 1-phenylazocane (472 mg, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (6.2 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture 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).

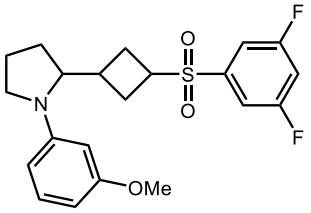
For the mixture of diastereomers:

^{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 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(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture 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).

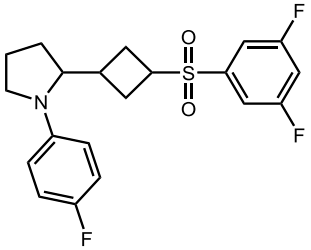
For the mixture of diastereomers:

^{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:

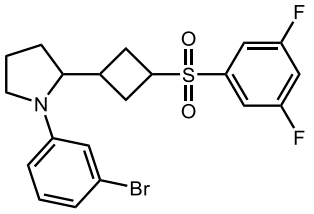
Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115 mg, 0.5 mmol, 1 equiv), 1-(4-fluorophenyl)pyrrolidine (413 mg, 2.5 mmol, 5 equiv), and [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture of diastereomers (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 diastereomers:

^{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 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 $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5.8 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture of diastereomers (130 mg, 57%

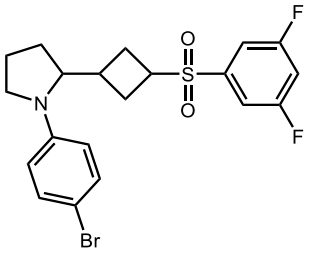
yield, 7:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear yellow oil after purification by flash column chromatography (10% ethyl acetate:hexanes).

For the mixture of diastereomers:

^{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 general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (73.0 mg, 0.32 mmol, 1 equiv), 1-(4-

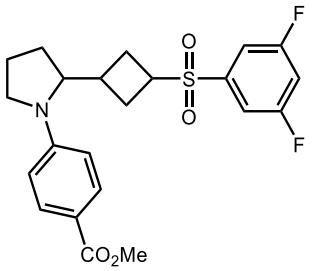
bromophenyl)pyrrolidine (360 mg, 1.6 mmol, 5 equiv), and [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (3.8 mg, 0.0032 mmol, 0.01 equiv) provided the product as a mixture of diastereomers (98 mg, 68% yield, 2:3 d.r. determined by NMR integral ratio of the bolded resonances below) as a clear brown oil after purification by flash column chromatography (10% ethyl acetate:hexanes).

For the mixture of diastereomers:

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.39z – 7.35 (m, 2H$_a$ + 2H$_b$), 7.25 – 7.20 (m, 2H$_a$ + 2H$_b$), 7.08 – 7.04 (m, 1H$_a$ + 1H$_b$), 6.45 (t, *J* = 9.6 Hz, 2H$_a$ + 2H$_b$), **3.83 – 3.77** (m, **1H$_a$ + 1H$_b$**), 3.61 (tt, *J* = 9.2, 4.5 Hz, 1H$_a$), 3.57 (ddd, *J* = 17.1, 9.4, 7.8 Hz, 1H$_b$), 3.46 (dt, *J* = 10.0, 5.0 Hz, 1H$_a$), 3.44 – 3.39 (m, 1H$_b$), 3.10 – 3.01 (m, 1H$_a$ + 1H$_b$), 2.98 – 2.91 (m, 1H$_a$), 2.58 – 2.41 (m, 1H$_a$ + 1H$_b$), 2.43 – 2.06 (m, 3H$_a$ + 4H$_b$), 2.06 – 1.86 (m, 3H$_a$ + 4H$_b$), 1.76 – 1.70 (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, 141.3, 131.8, 114.1, 113.9, 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, 22.8.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -104.82 (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:

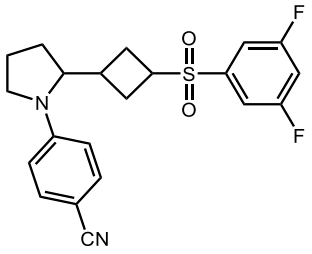
Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (115 mg, 0.5 mmol, 1 equiv), methyl 4-(pyrrolidin-1-yl)benzoate (513 mg, 2.5 mmol, 5 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (5 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture of 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 diastereomers:

^{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:

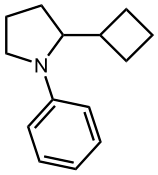
Following general procedure A, the reaction of 1-((3,5-difluorophenyl)sulfonyl)bicyclo[1.1.0]butane (114.6 mg, 0.5 mmol, 1 equiv), 4-(Pyrrolidin-1-yl)benzonitrile (432 mg, 2.5 mmol, 5 equiv), and [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (5.7 mg, 0.005 mmol, 0.01 equiv) provided the product as a mixture of diastereomers (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 diastereomers:

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)

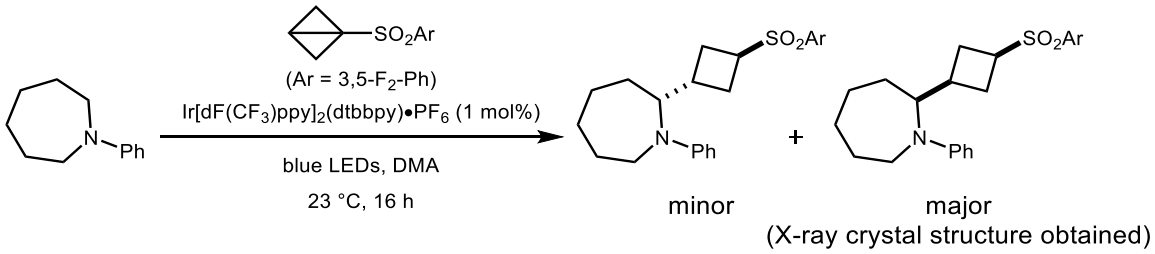


2-cyclobutyl-1-phenylpyrrolidine, 15: Following general procedure B, the reaction of 2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylpyrrolidine (140 mg, 0.38 mmol, 1 equiv) and magnesium turnings (380 mg, 15 mmol, 40 equiv) provided the product (54 mg, 71% yield) as a clear oil after purification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

5.5.6 X-Ray Crystallography Data



cis*-2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazepane, 7*cis and ***trans*-2-(3-((3,5-difluorophenyl)sulfonyl)cyclobutyl)-1-phenylazepane, 7*trans***: Following 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-phenylazepane (450 µl, 2.5 mmol, 5 equiv), and [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (6.4 mg, 0.005 mmol, 0.01 equiv) provided **7*cis*** (128.8 mg, 64% yield) as a clear oil and **7*trans*** (64 mg, 32% yield) as a clear oil after purification by flash column chromatography (0% ethyl acetate:hexanes to 20% ethyl acetate:hexanes). **7*cis*** R_f 0.26 (15% ethyl acetate:hexanes) **7*trans*** R_f 0.35 (15% ethyl acetate:hexanes); ^{1}H, ^{13}C, and ^{19}F data previously reported in "Procedure and Characterization Data" (section V). X-ray quality crystals were obtained for **7*cis*** from diethyl ether and hexane vapor diffusion.

X-Ray Crystallography Experimental: 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 minimization.

X-Ray Crystallography 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), $\alpha = \gamma = 90^{\circ}$, 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)

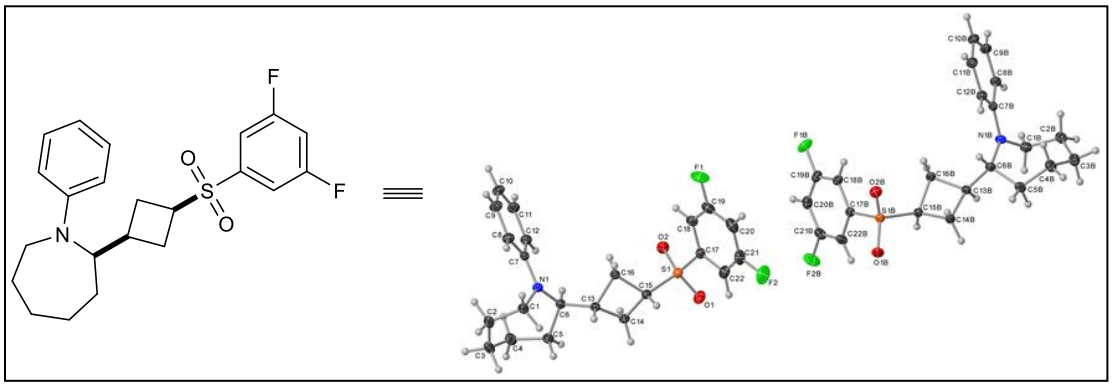


Figure S5.1. X-ray crystal structure of compound 7_{cis}. Black = carbon, grey = hydrogen, blue = nitrogen, red = oxygen, orange = sulfur, green = fluorine.

Appendix

Site-selective modification of jessenipeptin via α-amino radical conjugate addition

A-I Introduction

A global rise in multidrug-resistant bacteria has led to a growing demand for new antibiotics. Fewer novel modes of action combined with significant decrease in new approvals entering the market has led to physicians more commonly resorting to treatments that were previously seen as a last resort.[1] With increasing use, these drugs of last resort are in turn becoming less effective.[2] The urgent need for medicines to combat these deadly bacteria has been highlighted recently by the Centers for Disease Control who categorized it as a serious threat to society[3] and World Health Organization (WHO) who characterized it as a matter of utmost urgency.[4] Particularly vital are anti-Gram-negative therapeutics, as drug resistant Gram-negative bacteria comprise 75% of the priority pathogens list for the development of new antibiotics (as published by WHO).[5] Particular importance is placed on those strains of bacteria that are resistant to broad spectrum β-lactam based therapies and other treatments such as vancomycin,[6] tetracyclines,[7] and

[1] (a) Fosgerau, K.; Hoffmann, T. Peptide Therapeutics: Current Status and Future Directions. *Drug Discov. Today* **2015**, *20* (1), 122–128. (b) Panigrahi, K.; Eggen, M. J.; Maeng, J. H.; Shen, Q.; Berkowitz, D. B. The α,α-Difluorinated Phosphonate L-PSer-Analogue: An Accessible Chemical Tool for Studying Kinase- Dependent Signal Transduction. *Chem. Biol.* **2009**, *16* (9), 928–936. (c) Koch, G.; Yepes, A.; Förstner, K. U.; Wermser, C.; Stephanie, T.; Modamio, J.; Ohlsen, K.; Foster, K. R.; Lopez, D. Europe PMC Funders Group Evolution of Resistance to a Last-Resort Antibiotic in Staphyloccocus Aureus via Bacterial Competition. *Cell* **2015**, *158* (5), 1060–1071.

[2] (a) Llor, C.; Bjerrum, L. Antimicrobial Resistance: Risk Associated with Antibiotic Overuse and Initiatives to Reduce the Problem. *Ther. Adv. Drug Saf.* **2014**, *5* (6), 229–241. (b) Ramachandran, P.; Rachuri, N. K.; Martha, S.; Shakthivel, R.; Gundala, A.; Battu, T. S. Implications of Overprescription of Antibiotics: A Cross-Sectional Study *J. Pharm. Bioallied Sci*. **2019**, S434–S437.(c) CDC: 1 in 3 antibiotic prescriptions unnecessary. https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html. (accessed May 19, 2020).

[3] Biggest Threats and Data. https://www.cdc.gov/drugresistance/biggest-threats.html (accessed May 19, 2020).

[4] WHO Director-General briefs UN on antimicrobial resistance. https://www.who.int/dg/speeches/2016/antimicrobial-resistance-un/en/ (accessed May 19, 2020).

[5] Asokan, G. V.; Ramadhan, T.; Ahmed, E.; Sanad, H. WHO Global Priority Pathogens List: A Bibliometric Analysis of Medline-Pubmed for Knowledge Mobilization to Infection Prevention and Control Practices in Bahrain. *Oman Med. J.* **2019**, *34* (3), 184–193.

[6] Bruniera, F. R.; Ferreira, F. M.; Saviolli, L. R. M.; Bacci, M. R.; Feder, D.; Pedreira, M. D. L. G.; Peterlini, M. A. S.; Azzalis, L. A.; Junqueira, V. B. C.; Fonseca, F. L. A. The Use of Vancomycin with Its Therapeutic and Adverse Effects: A Review. *Eur. Rev. Med. Pharmacol. Sci.* **2015**, *19* (4), 694–700.

[7] Ian, C.; Marilyn, R. Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance. *Microbiol. Mol. Biol. Rev.* **2001**, *65* (3), 232–260.

fluoroquinolone.[8] Currently, cyclic lipopeptides (CLPs) such as the polymyxins (Polymyxin B1 + B2, Colistin A + B) are the therapeutic approaches of last resort.[9]

Key to the activity of the CLPs is the presence of the charged diaminobutyric acid (Dab) residues which bind competitively to membrane bound phosphates that allow recognition of the Gram-negative bacteria. The charged phosphate esters present on the outer membrane coating,

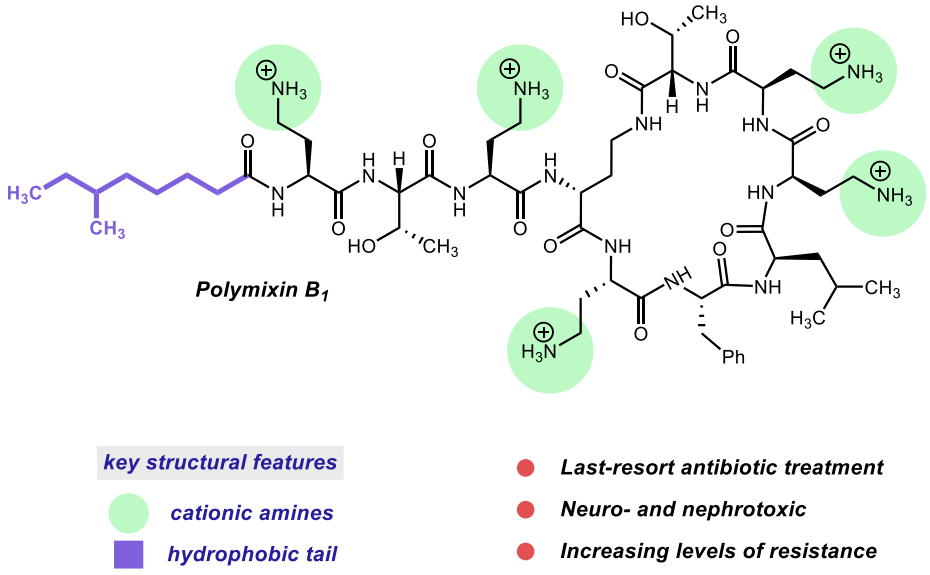


Figure A1. Polymyxin B1, a last resort antibiotic treatment, contains key structural features that lead to its antimicrobial potency

[8] Oliphant, C. M.; Green, G. M. Quinolones: A Comprehensive Review. *Am. Fam. Physician* **2002**, *65* (3), 455–464.
[9] (a) Kleijn L.H.J., Martin N.I. (2017) The Cyclic Lipopeptide Antibiotics. In: Fisher J., Mobashery S., Miller M. (eds) Antibacterials. Topics in Medicinal Chemistry, vol 26. Springer, Cham. (b) Schneider, T.; Müller, A.; Miess, H.; Gross, H. Cyclic Lipopeptides as Antibacterial Agents - Potent Antibiotic Activity Mediated by Intriguing Mode of Actions. *Int. J. Med. Microbiol.* **2014**, *304* (1), 37–43. (c) Bionda, N.; Pitteloud, J. P.; Cudic, P. Cyclic Lipodepsipeptides: A New Class of Antibacterial Agents in the Battle against Resistant Bacteria. *Future Med. Chem.* **2013**, *5* (11), 1311–1330.

or lipopolysaccharide (LPS), which are usually bound to Mg^{2+} or Ca^{2+} counterions typically present a barrier for cell penetration. The impermeability of the LPS is a primary reason for the difficulty in the development of anti-Gram-negative antibiotics. The presence of charged Dab residues in CLPs allows the displacement of the counterions, bringing the CLP in close contact with the membrane. The second key feature of these macrocyclic peptides is their lipophilicity. A high concentration of lipophilic amino acids in addition to a carbogenic pendant tail is required for membrane penetration and ultimately cell death. Although effective for the treatment of Gram-negative bacterial infections, the toxicity of these drugs is high, as is the probability that resistance to them will emerge, so the discovery of new anti-Gram-negative antibiotic therapies is imperative.

We recently discovered that aminoalkyl radicals, easily generated through sequential single electron oxidation and deprotonation of the acidified α-C–H bond, undergo highly effective intermolecular coupling with dehydroalanine (Dha) derivatives.[10] Through the use of photoredox catalysis,[11] this process operates with extremely high fidelity with respect to both the amine (radical precursor) and Dha (radical acceptor) systems to deliver α,γ-diaminobutyric acid residues that are structurally similar to the Dab residues observed in polymyxins. Antimicrobial peptides containing Dha or 2,3-dehydro-2-aminobutyric acid (Dhb) residues are common in nature.[12] Because radical methods have proved to be effective for the selective functionalization of α,β-unsaturated amino acid residues in peptides and proteins,[13] we questioned the ability of our method

[10] Aycock, R. A.; Pratt, C. J.; Jui, N. T. Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides. *ACS Catal.* **2018**, *8* (10), 9115–9119.

[11] (a)Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113* (7), 5322–5363. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81* (16), 6898–6926. (c) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116* (17), 10075–10166.

[12] Siodłak, D. α,β-Dehydroamino Acids in Naturally Occurring Peptides. *Amino Acids* **2015**, *47* (1), 1–17.

[13] (a) Wright, T. H.; Bower, B. J.; Chalker, J. M.; Bernardes, G. J. L.; Wiewiora, R.; Ng, W. L.; Raj, R.; Faulkner, S.; Vallée, M. R. J.; Phanumartwiwath, A.; Coleman, O. D.; Thézénas, M. L.; Khan, M.; Galan, S. R. G.; Lercher, L.; Schombs, M. W.; Gerstberger, S.; Palm-Espling, M. E.; Baldwin, A. J.; Kessler, B. M.; Claridge, T. D. W.; Mohammed, S.; Davis, B. G. Posttranslational Mutagenesis: A Chemical Strategy for Exploring Protein Side-Chain Diversity. *Science.* **2016**, *354* (6312),

for amino alkyl radical addition to forge new CLPs through selective functionalization of antimicrobial peptides containing these α,β-unsaturated residues. Moreover, we questioned the ability of this technology to reprogram the activity of antimicrobial CLPs (more specifically, to augment their activity against Gram negative microorganisms), as this semisynthetic approach would deliver peptides that contain the key features that lead to the potency of the polymyxin class of antibiotics.

To interrogate this hypothesis, we chose to study jessenipeptin, an antimicrobial CLP recently characterized by Stallforth.[14] Native jessenipeptin displays antibiotic activity towards nine different bacteria including MRSA and Pseudomonas aeruginosa, both of which are deemed to be serious threats to society.[3] Jessenipeptin also exhibits structural similarities to polymyxins, as it

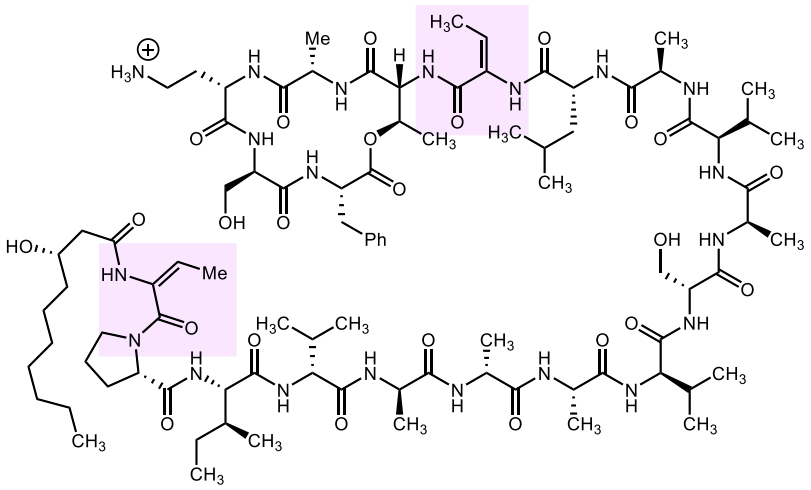


Figure A2. Antimicrobial CLP jessenipeptin contains two synthetically targetable Dhb residues

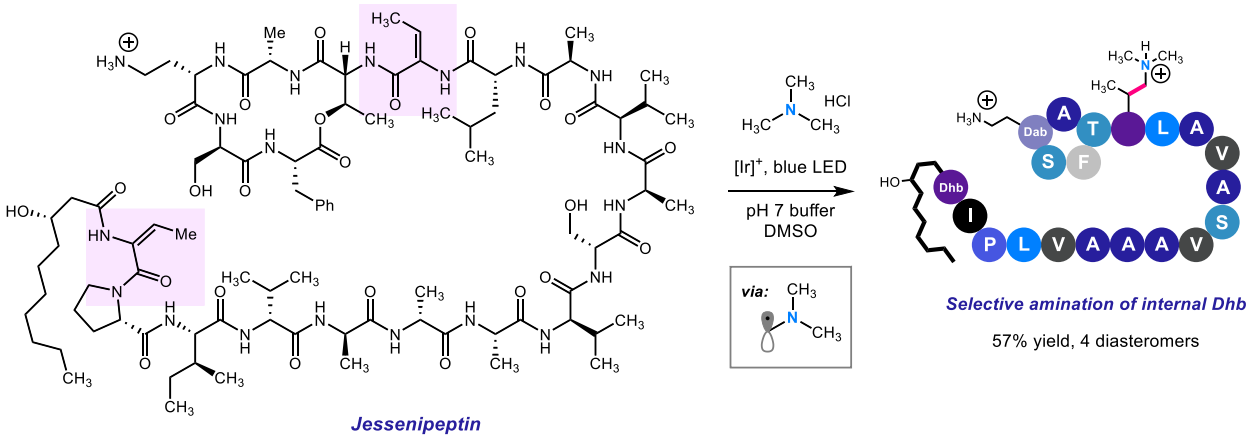
aag1465-1–11. (b) Yang, A.; Ha, S.; Ahn, J.; Kim, R.; Kim, S.; Lee, Y.; Kim, J.; Söll, D.; Lee, H. Y.; Park, H. S. A Chemical Biology Route to Site-Specific Authentic Protein Modifications. *Science.* **2016**, *354* (6312), 623–626.

[14] Arp, J.; Götze, S.; Mukherji, R.; Mattern, D. J.; García-Altares, M.; Klapper, M.; Brock, D. A.; Brakhage, A. A.; Strassmann, J. E.; Queller, D. C.; Bardl, B.; Willing, K.; Peschel, G.; Stallforth, P. Synergistic Activity of Cosecreted Natural Products from Amoebae-Associated Bacteria. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115* (15), 3758–3763.

contains numerous lipophilic residues and a carbogenic tail group in addition to as single Dab residue. Intriguingly, and of key importance to this work, jessenipeptin contains two Dhb residues which can be targeted for installation of amine groups to mimic the effects of the dab residues that influence the reactivity of polymyxin type antibiotics. Together, these features make jessenipeptin an ideal platform to showcase the utility of our method for radical-based peptide conjugation.

A-II Results and Discussion

Exposure of jessenipeptin to conditions very similar to those outlined in our previous report, using 300 equivalents of trimethylamine hydrochloride in a mixture of DMSO and aqueous sodium phosphate buffer, yielded 57% of the alkyl amine modified peptide as a mixture of four diastereomers by HPLC analysis. The mass balance consisted of a small amount of starting material in addition to demethylated addition product. Interestingly, inspection of the product by tandem mass spectrometry analysis showed complete selectivity for the internal Dhb residue.



Scheme A1. Synthetic modification of jessenipeptin via α-amino radical conjugate addition

Based on the SAR around the polymyxins we expect a significant increase in potency against Gram negative bacteria, but with a different toxicity and resistance profile to existing therapies.

A-III Conclusion

From these promising results and the pending biological assays, this technology may be applicable to the semi-synthetic reprogramming of other Dha (and related residues) containing CLPs. The possibility of addition of a second radical source to the remaining Dhb residue is currently unexplored but will be an avenue of future research to further explore the SAR around this promising antibiotic.

A-IV Experimental Information

General Information

Reactions were set up on the bench top and conducted under nitrogen atmosphere while subject to irradiation from blue LEDs (LEDwholesalers PAR38 Indoor Outdoor 16–Watt LED Flood Light Bulb). Jessenipeptin was isolated from a cell culture by the laboratory of Pierre Stallforth at the Leibniz Institute for Natural Product Research and Infection Biology.[15] Trimethylamine hydrochloride was purchased from Sigma Aldrich and used as received. Photocatalyst $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]_2 \bullet PF_6$ was prepared in accordance with a literature procedure.[15] DMSO was purchased from Sigma Aldrich and degassed by sonication under weak vacuum.

Procedure for synthetic modification of jessenipeptin

A screw-top test tube equipped with a stir bar was charged with jessenipeptin (10.0 mg, 5.25 µmol, 1.0 equiv), trimethylamine hydrochloride (150.4 mg, 1.57 mmol, 300 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 of 0.1 mg/mL $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (0.59 mg, 5.25 µmol, 1.0 equiv) in a mixture of degassed DMSO and 0.1M pH 7 sodium phosphate buffer by syringe (5.9 mL mL), . The resulting suspension was stirred under irradiation with blue LEDs for 16 hours. A 10 µL aliquot of the crude reaction mixture was submitted for LC-MS/MS analysis. Integration of the ion count signals that correspond to peptide-derived materials was indicative of a combined 57% yield of the observed jessenipeptin-NMe_3 adduct as a mixture of four diastereomers.

[15] Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-Electron Transmetalation in Organoboron Cross-Coupling by Photoredox/Nickel Dual Catalysis. *Science (80-.).* **2014**, *345* (6195), 433–436.

LC-MS/MS Data for jessenipeptin-NMe$_3$ adduct

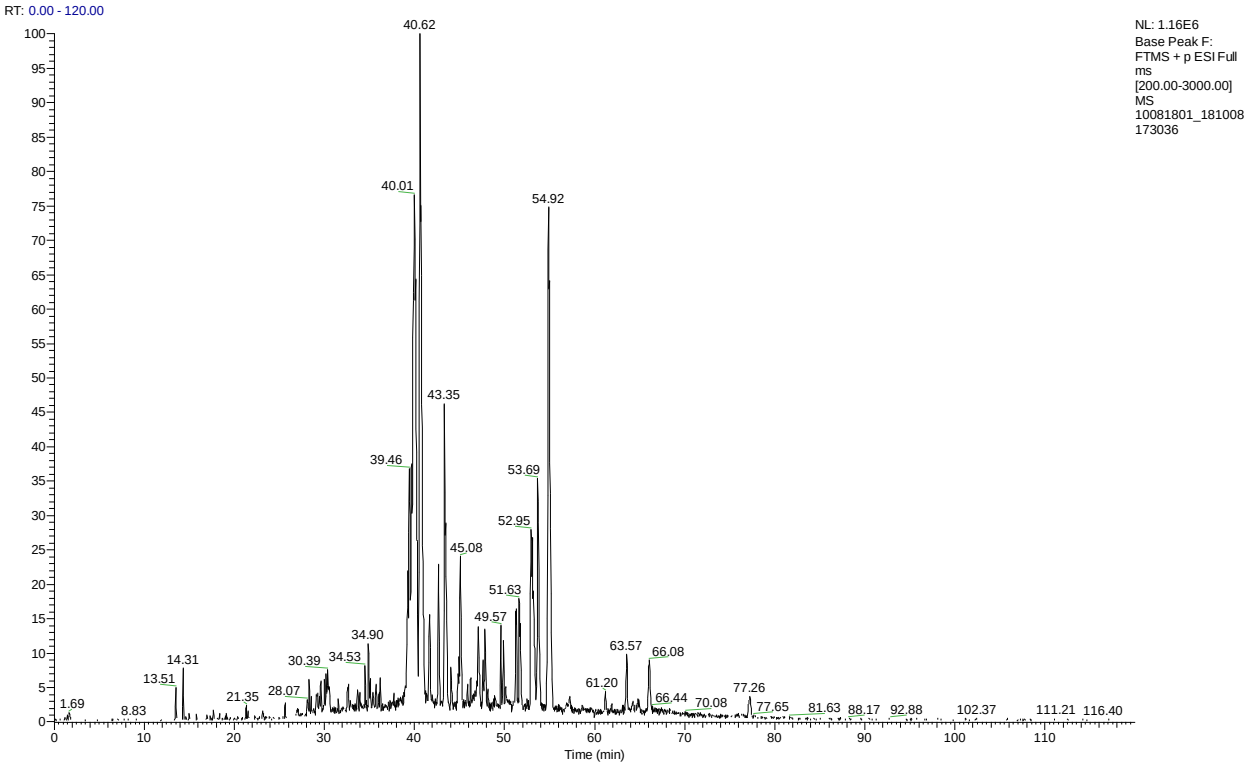


Figure A-S1. Analytical liquid chromatogram of conjugate addition reaction with jessenipeptin

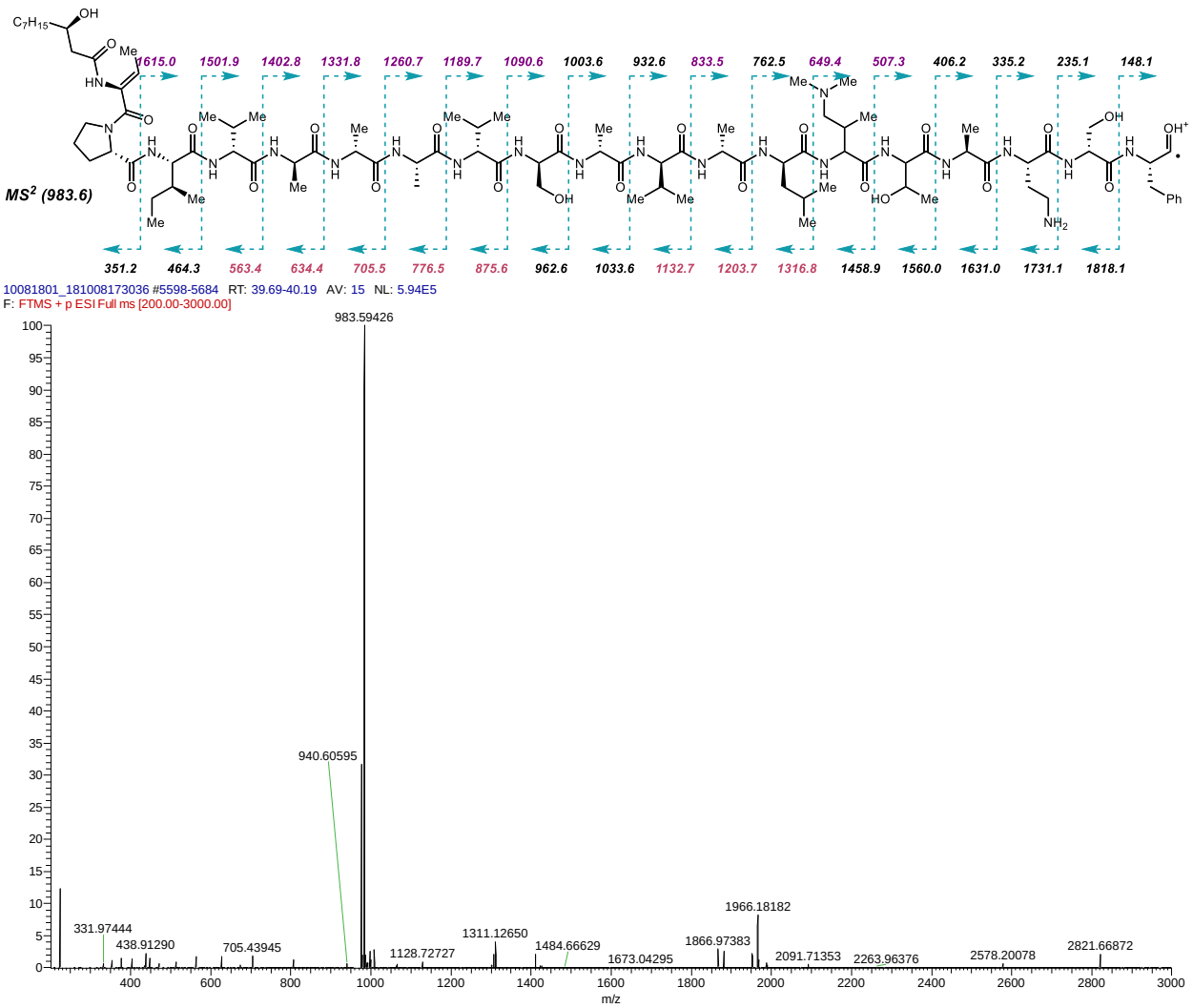


Figure A-S2. LC-MS Analysis of jessenipeptin-NMe$_3$ adduct

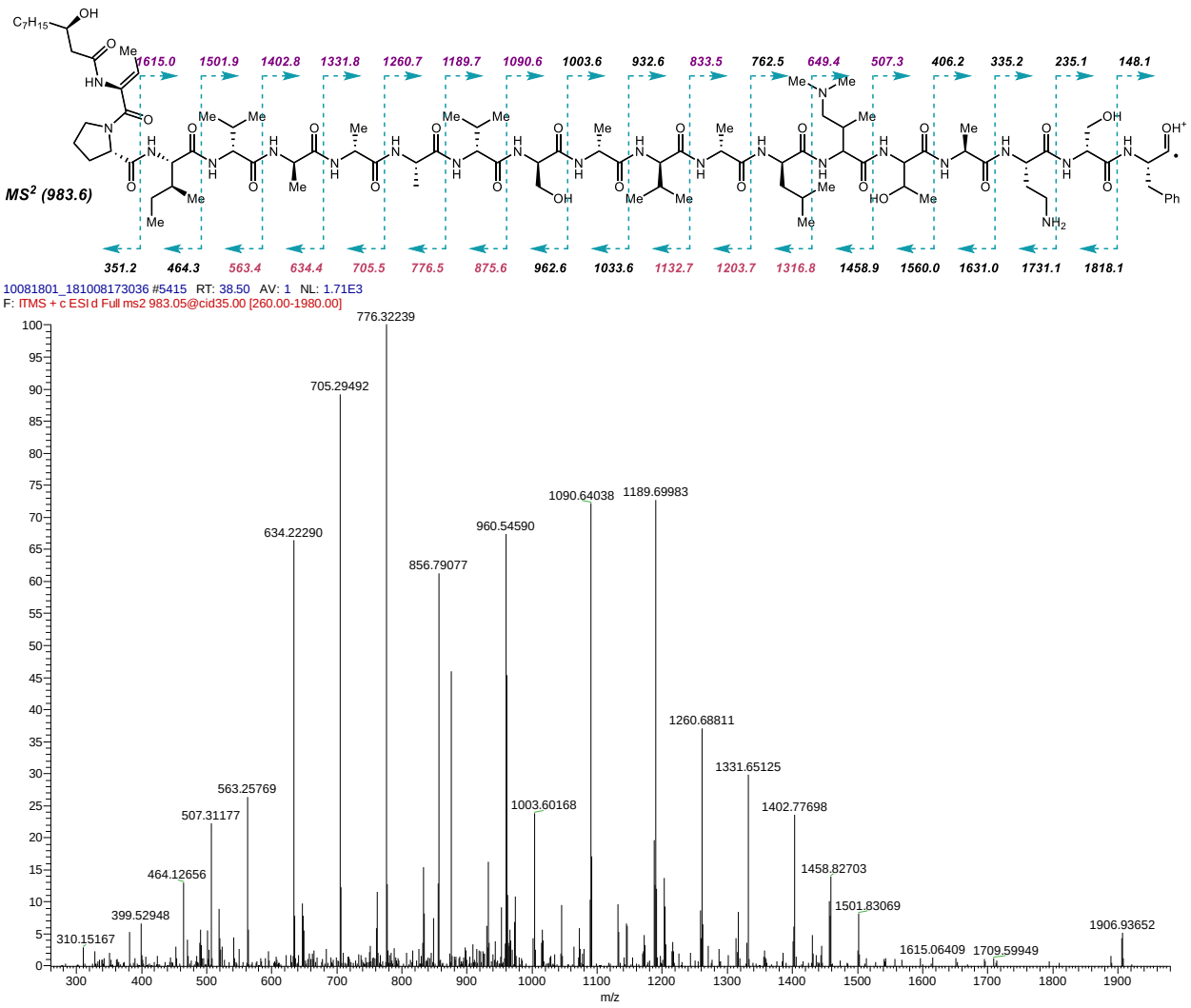


Figure A-S3. LC-MS/MS analysis of jessenipeptin-NMe$_3$ adduct

Integration of LC-MS/MS Analysis of jessenipeptin-NMe$_3$ adduct

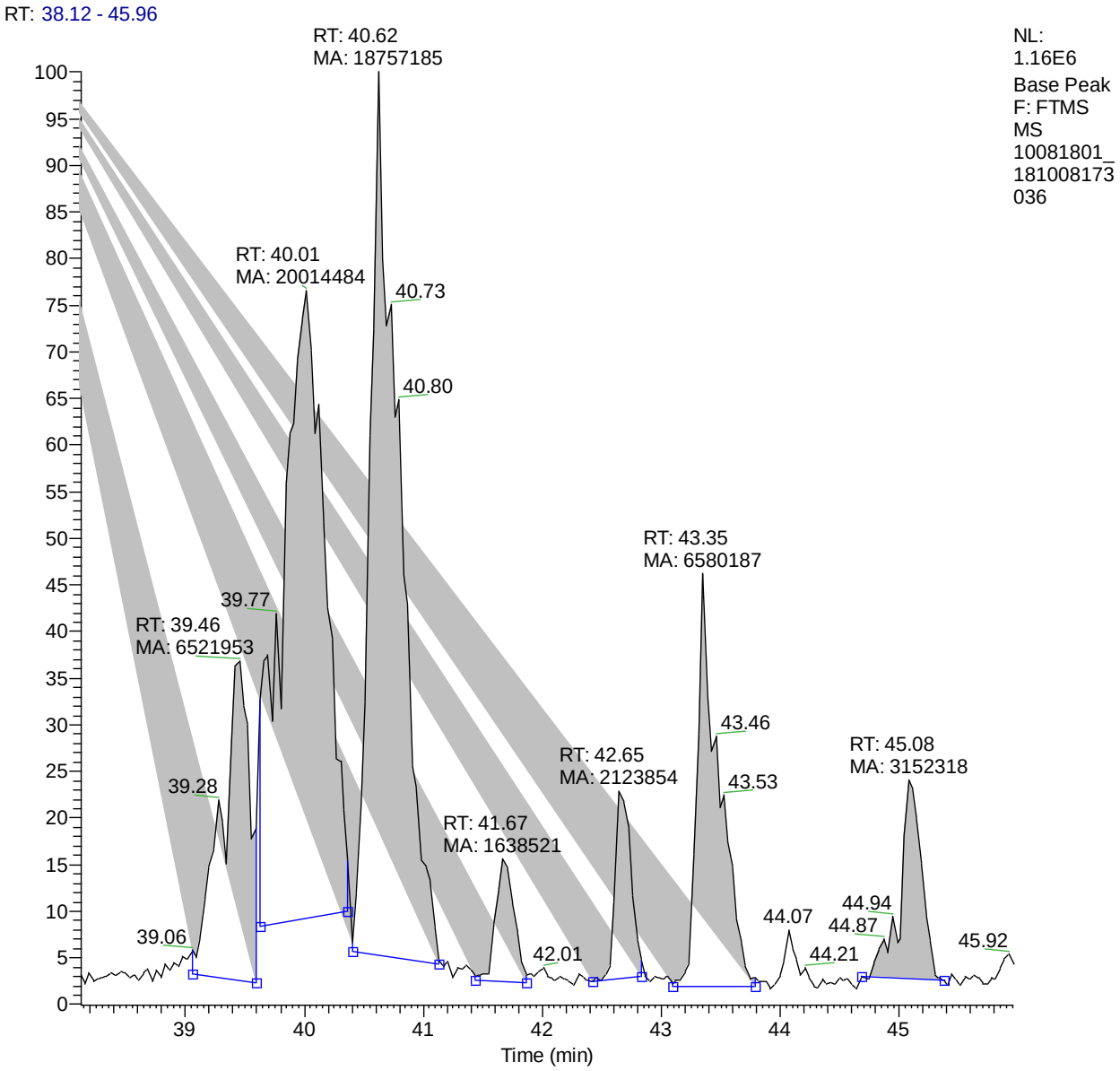


Figure A-S4. Integrated HPLC Zoom 38 – 46 min

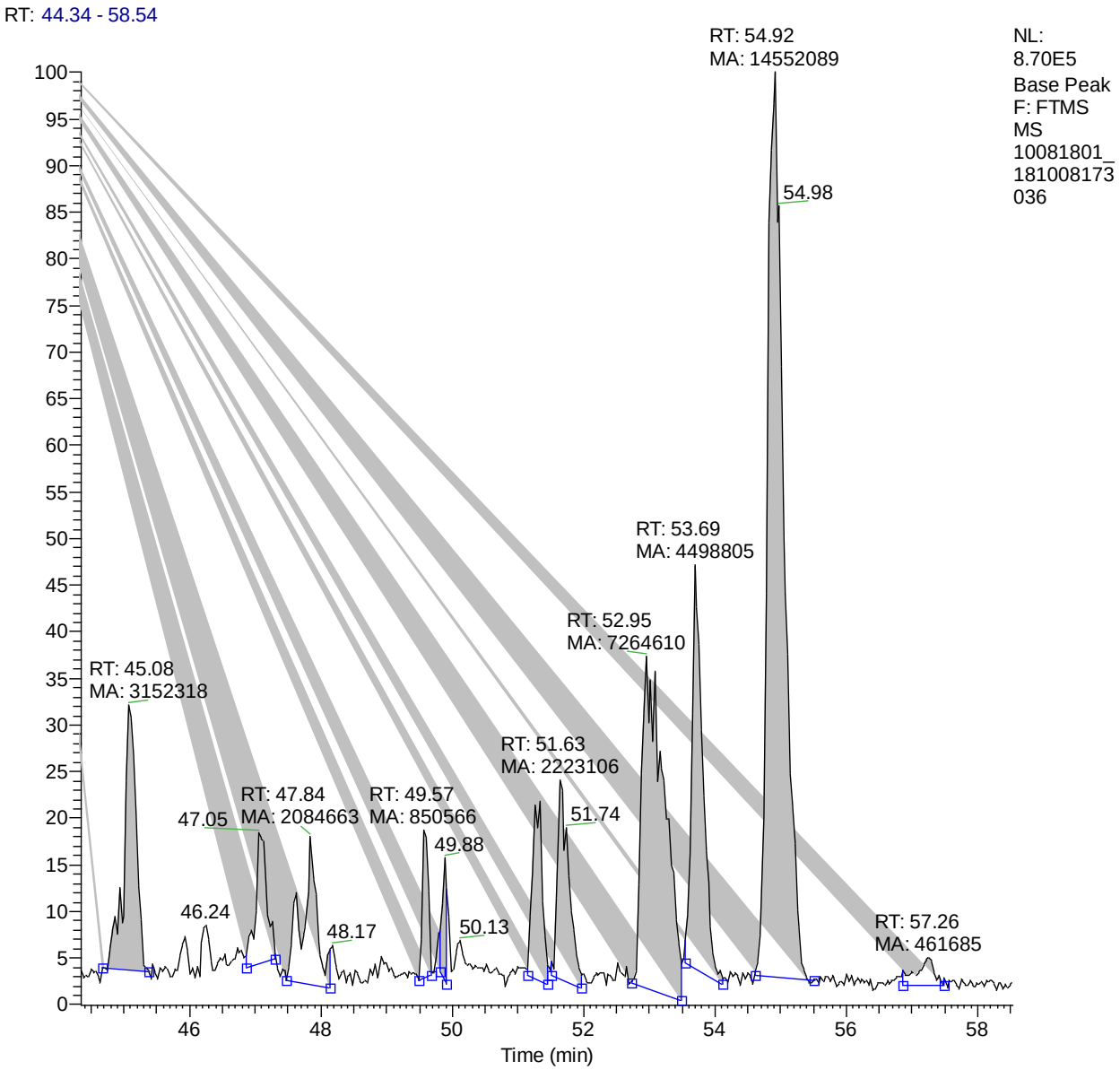


Figure A-S5. Integrated HPLC Zoom 44 – 59 min

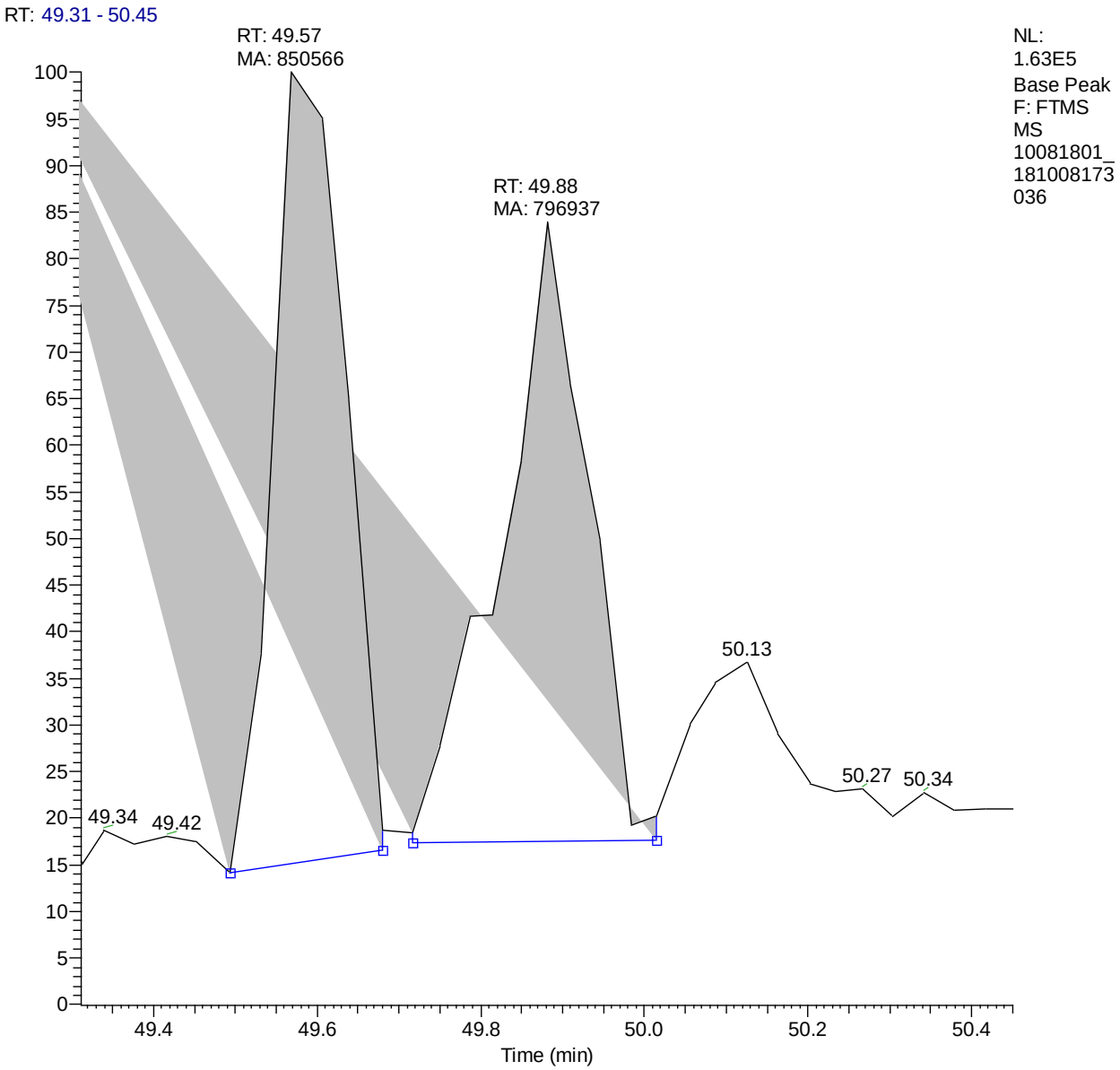


Figure A-S6. Integrated HPLC Zoom 49 – 50 min

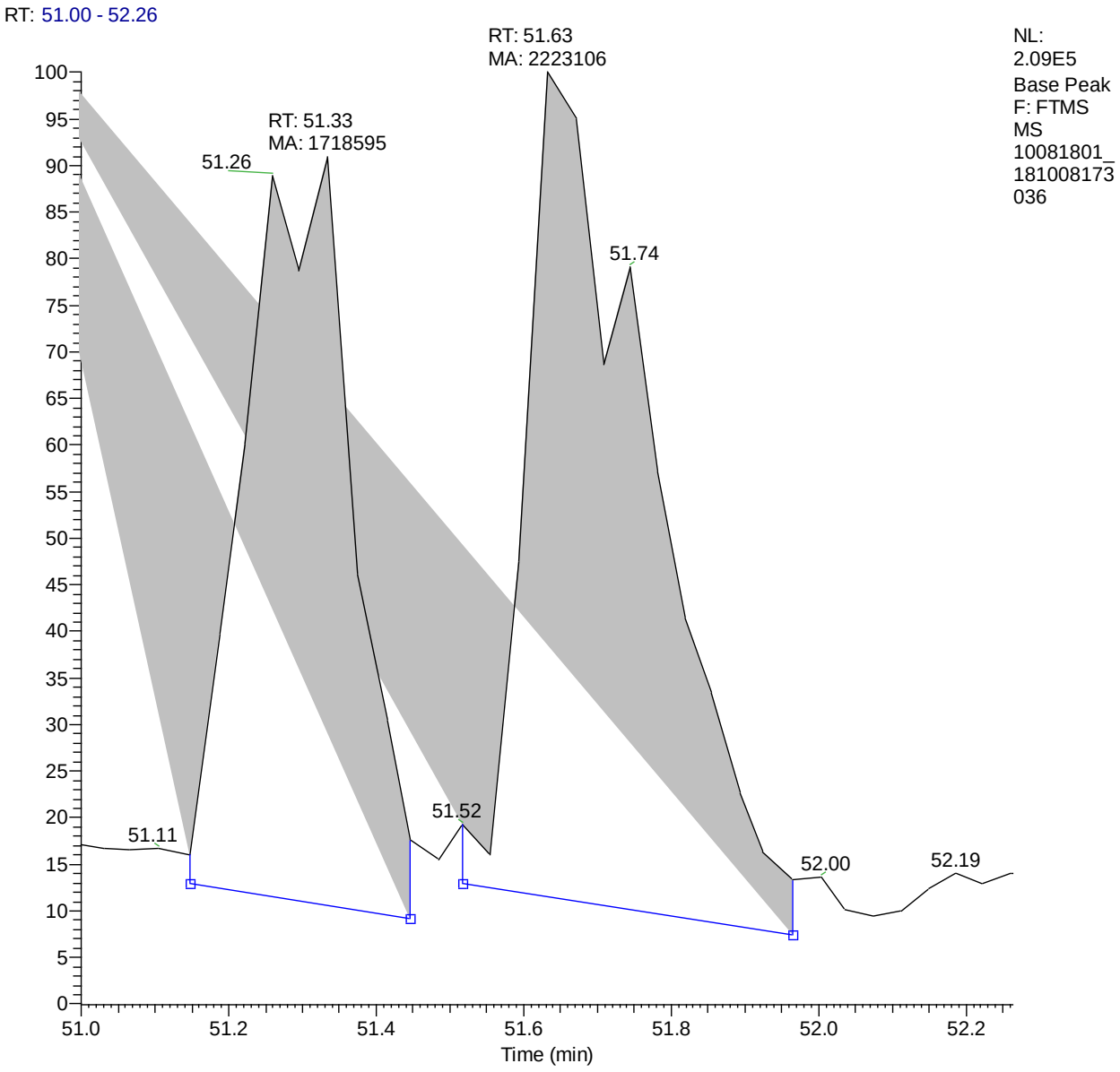


Figure A-S7. Integrated HPLC Zoom 51 – 52 min