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A Redox Auxiliary Strategy for Pyrrolidine Synthesis via Photocatalytic [3+2] Cycloaddition

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Abstract

Cycloaddition reactions can be used to efficiently assemble pyrrolidine rings that are significant in a variety of chemical and biological applications. We have developed a method for the formal cycloaddition of cyclopropyl ketones with hydrazones that utilizes photoredox catalysis to enable the synthesis of a range of structurally diverse pyrrolidine rings. The key insight enabling the scope of photoredox [3+2] cycloadditions to be expanded to C=N electrophiles was the use of a redox auxiliary strategy that allowed for photoreductive activation of the cyclopropyl ketone without the need for an exogenous tertiary amine co-reductant. These conditions prevent the deleterious reductive ring-opening of the cyclopropyl substrates, enabling a range of less-reactive coupling partners to participate in this cycloaddition.

Graphical Abstract

A radical solution. A photoredox protocol for formal [3 + 2] cycloaddition of cyclopropyl ketones and hydrazones has been developed. The photocatalytically generated distonic radical anion intermediate can efficiently engage relatively unreactive C=N bonds only when the reaction conditions are tuned to obviate the need for an amine co-reductant.

Keywords

cycloaddition; heterocycles; photocatalysis; radical ions; small ring systems

Introduction

Pyrrolidines feature prominently in wide variety of bioactive natural products and pharmaceutical compounds.¹ The importance of these ring systems has motivated the development of a wide variety of strategies for their construction.² Cycloadditions have been

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particularly valued for their capacity to assemble structurally complex, densely functionalized pyrrolidines with high efficiency (Figure 1). The most well-developed cycloaddition methods for pyrrolidine synthesis are reactions of azomethine ylides and related 1,3-dipoles.³ Somewhat less well-developed but nevertheless widely utilized are formal [3 + 2] cycloadditions between imines and donor-acceptor cyclopropanes.⁴

We speculated that photoredox catalysis might offer an alternate disconnection to complement these existing cycloaddition methodologies. Our laboratory recently demonstrated that diverse cyclopentanes are accessible via formal [3 + 2] cycloadditions between aryl cyclopropyl ketones and alkenes.⁵ These methods exploit a dual Lewis acid-photoredox catalyst system that results in the photoreductive generation of a ring-opened distonic radical anion as the key reactive intermediate. We reasoned that if these intermediates could be intercepted by imines as reaction partners instead of alkenes, the resulting method would be an attractive new route to the production of five-membered nitrogen heterocycles. However, substituting highly polarized C=X bonds for olefins in reaction methods is rarely a straightforward process, and exploratory experiments demonstrated that the methods we had developed for the [3+2] synthesis of cyclopropanes did not smoothly translate to the synthesis of pyrrolidines. This objective therefore requires a modified approach. The results of our exploratory experiments towards this goal are reported herein.

Results and Discussion

Our initial investigations screened several combinations of cyclopropyl ketones (e.g., **1**) and imine coupling partners (**2**) using conditions we had previously reported for the analogous photoredox [3 + 2] synthesis of cyclopentane rings. In those cases where new pyrrolidine products were observed, the yields were relatively low, and they were accompanied by the production of ring-opened compounds arising from the reductive cleavage of the cyclopropyl ketone (Scheme 1). To account for this observation, we conducted a more thorough analysis of the intermediates involved in this reaction. Visible light promoted excitation of Ru(bpy)₃²⁺ affords an excited state that undergoes reductive quenching by *i*-Pr₂NEt. The resulting Ru(I) complex is a stronger reductant than Ru*(bpy)₃²⁺. We have speculated that the Ru(I) complex is the species that reduces the Lewis-acid-bound ketone to afford the activated distonic radical anion intermediate **4**, which is the key intermediate leading to productive cycloaddition. However, *i*-Pr₂NEt itself is also a competent terminal reductant in photoredox reactions.⁶ If the productive reaction between **4** and its reaction partner is relatively slow, we speculated that overreduction of **4**, either by *i*-Pr₂NEt or a related species derived from its oxidation⁷ could produce ring-opened product **5**.

The role of *i*-Pr₂NEt in our original reaction design was to quench Ru(bpy)₃²⁺ to produce a longer-lived, more strongly reducing Ru(I) complex. The desired [3 + 2] cycloaddition, however, is an isohypsic transformation overall, and thus a terminal reductant is not required for a balanced reaction scheme. Moreover, tertiary amines can be ligands for Lewis acidic metal centers, including the lanthanoid Lewis acids that have proven to be optimal in our studies. The formation of these Lewis acid-base complexes can be deleterious to the overall rate of dual Lewis acid-photoredox catalytic reactions.^{5b} This analysis suggested that the

reactivity of this system might be substantially improved by developing conditions that could operate without the need for an exogenous amine as a reductive quencher.

We reasoned that the need for the amine would be circumvented by designing a new reaction system with two key features: (1) a substrate with a more positive reduction potential than phenyl cyclopropyl ketones, and (2) a photocatalyst with an intrinsically more negative excited state reduction potential than $\text{Ru}(\text{bpy})_3^{2+}$.⁸ These changes would enable the design plan outlined in Scheme 2. Visible light photoexcitation of a strongly reducing photocatalyst to its triplet state would trigger one-electron reduction of a Lewis acid-activated cyclopropyl ketone (**A**). Reversible ring-opening of the ketyl radical (**A**^{•−}) would afford distonic radical anion **B**^{•−}. In the absence of a competitive reductant, we propose that the lifetime of this intermediate will be sufficiently long to undergo productive [3 + 2] cycloaddition with less-reactive imine reaction partners without deleterious overreduction. The resulting product radical anion (**C**^{•−}) could result in the formation of product **C** by either participating in chain-propagating reduction of another equivalent of the Lewis acid bound cyclopropyl ketone substrate or by regenerating the photocatalyst by back electron transfer to its oxidized state. Key to the realization of this design plan would be the identification of a combination of cyclopropyl ketone and photocatalyst that could photogenerate the desired radical anion intermediate without the need for a tertiary amine co-reductant.

To satisfy the requirement for a more easily reduced substrate, we considered the use of a “redox auxiliary,” which our laboratory recently defined as a cleavable moiety that can be temporarily installed to modulate the redox properties of a given substrate.⁹ Our initial demonstration of the utility of this concept was in the design of a photocatalytic [2 + 2] enone cycloaddition,^{9a} and we hypothesized that this strategy might also prove to be enabling in the context of a [3 + 2] cycloaddition as well. In particular, we surmised that cyclopropyl heteroaryl ketones bearing additional coordination sites would exhibit a stronger binding affinity for a Lewis acid co-catalyst and thus exhibit a more pronounced change in reduction potential when coordinated. To test this hypothesis, we performed a series of cyclic voltammetry (CV) studies for three model arylcyclopropanes with and without added Lewis acid (Table 1). In all cases, an irreversible reduction was observed in the absence of Lewis acid. Approximate $E_{p/2}$ values were determined using the method described by Nicewicz.¹⁰ The most electron-rich ketone (2-imidazolyl) proved to be the hardest to reduce, and the most electron-deficient (2-pyridyl) the easiest. When these CV studies were repeated in the presence 1 equiv of $\text{Sc}(\text{OTf})_3$, new features were observed in each voltammogram, the apparent $E_{p/2}$ potentials of the heteroaromatic ketones shifted to significantly more positive reduction potentials than the phenyl auxiliary. This effect is consistent with the greater propensity of the chelating heteroaryl ketones to coordinate strongly to a Lewis acid catalyst. Encouragingly, the Lewis acid-shifted potentials of the heteroaryl ketones were both within the range of the excited state reduction potential of many heteroleptic and homoleptic iridium photocatalysts.

We therefore hypothesized that the direct, amine-free photoredox activation of aryl cyclopropyl ketones would be significantly facilitated by the use of a heteroaryl redox auxiliary group. To test this premise, we examined these ketones in a model [3 + 2] cycloaddition with styrene using $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ ($E_0(\text{PC}^+/\text{PC}^*) = -0.98 \text{ V vs. SCE}$) as

photocatalyst and $\text{Sc}(\text{OTf})_3$ as a Lewis acid. While the parent phenyl cyclopropyl ketone was completely unreactive under these conditions (Table 1, entry 1), consistent with the electrochemical data, the 2-imidazolyl and 2-pyridyl cyclopropyl ketones afforded good yields of the [3 + 2] cycloadduct in the absence of reductive quencher (entries 2 and 3). The 2-imidazolyl ketone provided the highest yield, and we elected to continue our investigations using this auxiliary group.

We next turned our attention to identifying an optimal photocatalyst for the [3 + 2] cycloaddition reaction between cyclopropyl imidazolyl ketones and imines. Because the cyclopropyl ketone substrate would need to interact directly with the short-lived excited state of the photocatalyst, we predicted that its identity would have a significant effect on the rate of the cycloaddition. Thus, we prepared a series of photocatalysts spanning a range of excited-state redox potentials¹¹ and assessed their ability to promote a model [3 + 2] cycloaddition between imidazolyl ketone **9** and glyoxalate oxime ether **10** in the absence of an amine quencher (Table 2). As expected, there is a relationship between the excited state reduction potential of the photocatalyst and the rate of the reaction: in general, more strongly reducing photocatalysts provided higher yields. Interestingly, this was not true of the Ir photocatalysts with the most negative excited state reduction potentials ($\text{Ir}(\text{3-tBuppy})_3$ and $\text{Ir}(\text{ppy})_3$), which resulted in significantly diminished yields (entries 10 and 11). These two strongly reducing photocatalysts have a correspondingly much less positive ground-state reduction potential. Because the reaction mechanism proposed in Scheme 2 requires a reduction step to regenerate the active photocatalyst, this observation would be consistent with a change in rate-determining step where catalyst turnover is slowed due to increased stabilization of the Ir(IV) oxidation state. Thus the optimal photocatalyst that emerged from this screen was not the most electron-rich photocatalyst but instead the homoleptic iridium complex bearing 4- CF_3 ppy ligands (entry 8).

Having identified an appropriate combination of redox auxiliary and photocatalyst that enables photoreductive direct activation of cyclopropyl ketones, we conducted a routine investigation of reaction parameters to optimize the yield of the pyrrolidine cycloadduct. The effect of key variables on the reaction are summarized in Table 3. Hydrazone **12** was a more efficient coupling partner than the analogous oxime ether, though a decrease in diastereoselectivity was observed. Using $\text{Yb}(\text{OTf})_3$ as a Lewis acid instead of $\text{Sc}(\text{OTf})_3$ provided an increase in diastereoselectivity (entry 6), which was further improved by performing the reaction in THF instead of CH_2Cl_2 and by increasing the loading of $\text{Yb}(\text{OTf})_3$ (Entries 4 and 5). Further improvements in rate and selectivity were observed upon the addition of a desiccant (MgSO_4) and using a more intense light source (entries 2 and 3). Finally, there was an unexpected increase in d.r. at higher loadings of hydrazone to provide cycloadduct **13** in 85% yield and 5:1 d.r. after 8 h (entry 1).¹² Control studies verified the requirement of all reaction components for productive reactivity.

Figure 2 summarizes experiments probing the scope of this process under optimized conditions. The scope with respect to the β -aryl substituent was relatively general. Electron-rich aryl rings were well tolerated in good yields and modest diastereoselectivities (**14** and **15**). Very electron-deficient aryl rings were also well tolerated in good yields and good to excellent diastereoselectivities (**16** and **17**). A potentially reactive aryl bromide was well

tolerated under these conditions (**18**), and placing steric bulk in the *ortho* position of the aromatic ring was also well tolerated (**19**). Both electron-deficient and electron-rich heteroaryl-substituted cyclopropanes were viable substrates (**20** and **21**), though Lewis basic moieties such as pyridine rings that could compete for the Lewis acid co-catalyst result in reduced yields. Trisubstituted cyclopropanes exhibited excellent regioselectivity and good diastereoselectivities under these conditions (**22**), although these reactions were relatively sluggish. A more electron-deficient cyclopropane derivative with an ester substituent was also a viable substrate in this transformation (**23**). This result highlights the generality that can be accessed by exploiting radical intermediates: both electron-withdrawing and electron-donating substituents are well tolerated. As suggested by our earlier experiments while exploring redox auxiliaries, a 2-pyridyl cyclopropyl ketone also shows productive reactivity in this transformation (**24**). The substrate scope for imine derivatives proved to be significantly more limited. A formaldehyde-derived hydrazone was an excellent substrate under these conditions (**25**). A ketimine derived from ethyl pyruvate showed productive reactivity to generate a quaternary stereocenter (**26**), although the rate of this reaction was significantly diminished. Acetaldehyde-derived hydrazones produced intractable mixtures of products; however, the benzyl oxime ether derived from acetaldehyde was an excellent coupling partner in this transformation and afforded modest yields and high diastereoselectivities (**27**).

Finally, we investigated conditions that might be able to convert the cycloadducts to simpler pyrrolidines. Although several methods for the cleavage of hydrazines and hydrazides via the reduction of N–N bonds have been developed,¹³ the reductive scission of fully substituted hydrazines is an unsolved problem. An extensive screen of reported conditions revealed that the imidazolyl ketone was sensitive to these strongly reducing conditions. Alternatively, several reports have described the removal *C*-acylimidazolyl moieties via *N*-methylation of the imidazole followed by displacement of the resulting N-heterocyclic carbene to afford acids, esters, and amides.¹⁴ However, the nucleophilic hydrazine moiety proved to undergo competitive alkylation and complicated this cleavage strategy. Ultimately, we were unable to identify a set of reaction conditions that could controllably cleave either of these functional groups in synthetically useful yields. Future work to develop this study into a practical method for pyrrolidine synthesis, therefore, will focus on the investigation of conditions to engage alternate radicalophilic imine reaction partners that might result in more readily cleaved N-substituents. These studies will be facilitated by the central insight of the studies described above, which is that the use of a problematic tertiary amine co-reductant in photoredox reactions can be obviated by rational tuning of the relative electrochemical properties of the substrate and photocatalyst.

Conclusions

We have determined that tertiary amine co-reductants that are commonly utilized to facilitate electron transfer in photoredox catalysis can have unintended deleterious side effects. In particular, they can interfere with redox-neutral cycloaddition reactions by promoting undesired overreduction processes. We have shown that these issues can be circumvented by using a photocatalyst with a more negative excited state reduction potential in conjunction with a modified substrate that is more susceptible to one-electron reduction. We have shown

that this strategy enables the photoreductively triggered formal [3+2] cycloaddition of aryl cyclopropyl ketones with relatively unreactive hydrazone radicalophiles. We anticipate that the implementation of these insights to other photoredox processes could have a similar beneficial impact on the scope of reactions in this increasingly important class of synthetically useful transformations.

Experimental Section

General procedure for [3 + 2] cycloadditions with hydrazones

A 25 mL Schlenk tube was charged with MgSO_4 (100 wt%) and flame-dried under vacuum. A separate flame-dried vial was charged with cyclopropane (1 equiv), hydrazone (2 equiv), $\text{Yb}(\text{OTf})_3$ (1 equiv), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (0.01 equiv) and THF (0.1 M). The vial was briefly sonicated until homogenous, the contents were transferred to the cooled Schlenk tube, and the Schlenk tube was sealed. The reaction mixture was degassed by three freeze-pump-thaw cycles and then backfilled with nitrogen. The reaction vessel was placed 15 cm away from a 34 W blue LED (Kessil) and irradiated for the indicated time. After this time, the reaction mixture was diluted with EtOAc and extracted with H_2O . The aqueous phase was extracted once with EtOAc, and the combined organics were washed with 10% aq. K_2CO_3 and brine. The organic layer was then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The cycloadduct was then purified by column chromatography.

Ethyl 5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)-3-phenylpyrrolidine-2-carboxylate (13)

Reaction was carried out according to the general procedure with (1-methyl-1H-imidazol-2-yl)(2-phenylcyclopropyl)methanone (91.0 mg, 0.4 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), $\text{Yb}(\text{OTf})_3$ (248.0 mg, 0.4 mmol), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 8 hours giving the crude product as a yellow oil (5:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/ NET_3 then 2:3 acetone/pentanes) to give the pure product as a white solid (140 mg, 0.34 mmol, 85 % yield). Relative stereochemistry determined by single crystal X-ray crystallography.¹² ^1H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.14 (m, 5H), 7.14 (s, 1H), 7.04 (s, 1H), 5.69 (dd, *J* = 9.5, 8.4 Hz, 1H), 4.89 (d, *J* = 9.2 Hz, 1H), 4.25 (dtd, *J* = 21.1, 8.6, 7.0 Hz, 2H), 4.13 – 3.97 (m, 2H), 4.05 (s, 3H), 3.91 (td, *J* = 8.9, 7.5 Hz, 1H), 3.74 (dq, *J* = 9.3, 6.4, 5.7 Hz, 1H), 3.66 (dq, *J* = 10.7, 7.1, 6.4 Hz, 1H), 3.10 (dt, *J* = 13.0, 8.5 Hz, 1H), 2.20 (ddd, *J* = 13.0, 9.6, 7.3 Hz, 1H), 0.79 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 189.2, 170.7, 155.5, 142.0, 140.9, 129.6, 128.4, 128.1, 127.0, 126.9, 67.7, 66.4, 62.3, 60.3, 46.4, 44.6, 36.1, 35.8, 13.6. M.p. 151–154.5 °C. HRMS (ESI) calculated for $[\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}_5]^+$ { M^+H^+ } requires 413.1820, found 413.1820.

Ethyl 3-(4-methoxyphenyl)-5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)pyrrolidine-2-carboxylate (14)

Reaction was carried out with a modified version of the general procedure with (2-(4-methoxyphenyl)cyclopropyl)(1-methyl-1H-imidazol-2-yl)methanone (104.8 mg, 0.41 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), $\text{Yb}(\text{OTf})_3$ (76.0 mg, 0.123 mmol, 0.3 equiv.), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (3.4 mg, 0.004 mmol), and THF (4 mL).

The reaction was complete after 8 h giving the crude product as a yellow oil (2:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ then 2:3 acetone/pentanes) to give the pure product as a white solid (109 mg, 0.25 mmol, 60% yield). Major Diastereomer: ¹H NMR (500 MHz, Chloroform-d) δ 7.18 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 0.9 Hz, 1H), 7.07 (d, J = 0.8 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 5.58 (dd, J = 9.1, 1.7 Hz, 1H), 4.50 (d, J = 8.0 Hz, 1H), 4.28 – 4.14 (m, 4H), 4.08 (dt, J = 11.6, 7.8 Hz, 1H), 4.01 (s, 3H), 3.85 – 3.76 (m, 4H), 3.70 (dq, J = 10.7, 7.2 Hz, 1H), 3.65 – 3.59 (m, 1H), 2.67 (td, J = 12.1, 9.1 Hz, 1H), 2.54 (ddd, J = 12.5, 7.6, 1.8 Hz, 1H), 0.85 (t, J = 7.2 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 188.9, 172.3, 158.8, 157.7, 143.6, 129.8, 129.2, 129.0, 127.7, 113.6, 69.0, 61.7, 60.5, 59.7, 55.3, 43.8, 41.0, 36.0, 29.5, 13.7. M.p. 186.1–184.3 °C. HRMS (ESI) calculated for [C₂₂H₂₇N₄O₆]⁺{M⁺H⁺} requires 443.1925, found 443.1925.

Ethyl 3-(3-methoxyphenyl)-5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)pyrrolidine-2-carboxylate (15)

Reaction was carried out with the general procedure with (2-(3-methoxyphenyl)cyclopropyl)(1-methyl-1H-imidazol-2-yl)methanone (103.2 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), Yb(OTf)₃ (248.0 mg, 0.40 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 8 hours giving the crude product as a yellow oil (3.5:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ then 2:3 acetone/pentanes) to give the pure product as a colorless oil (150.2 mg, 0.34 mmol, 84 % yield). ¹H NMR (500 MHz, Chloroform-d) δ 7.16 – 7.10 (m, 2H), 7.03 (d, J = 0.9 Hz, 1H), 6.93 (dd, J = 2.5, 1.7 Hz, 1H), 6.85 (dt, J = 7.6, 1.3 Hz, 1H), 6.72 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H), 5.66 (t, J = 8.9 Hz, 1H), 4.89 (d, J = 8.9 Hz, 1H), 4.32 – 4.18 (m, 2H), 4.10 (ddd, J = 9.4, 8.3, 7.2 Hz, 1H), 4.06 – 3.98 (m, 4H), 3.87 (td, J = 8.9, 7.0 Hz, 1H), 3.81 – 3.69 (m, 5H), 3.11 (dt, J = 13.1, 8.7 Hz, 1H), 2.18 (ddd, J = 13.1, 9.1, 6.9 Hz, 1H), 0.83 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 189.3, 170.6, 159.4, 155.5, 142.6, 142.0, 129.6, 129.0, 127.0, 120.7, 113.5, 112.9, 67.6, 66.4, 62.3, 60.3, 55.2, 46.4, 44.7, 36.0, 35.8, 13.7. HRMS (ESI) calculated for [C₂₂H₂₇N₄O₆]⁺{M⁺H⁺} requires 443.1925, found 443.1925.

Ethyl 5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (16)

Reaction was carried out with the general procedure with (1-methyl-1H-imidazol-2-yl)(2-(4-(trifluoromethyl)phenyl)cyclopropyl)methanone (121.3 mg, 0.41 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), Yb(OTf)₃ (248.0 mg, 0.40 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 12 hours giving the crude product as a yellow oil (5:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ then 2:3 acetone/pentanes) to give the pure product as a white solid (168.1 mg, 0.35 mmol, 85 % yield). ¹H NMR (500 MHz, Chloroform-d) δ 7.51 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 0.9 Hz, 1H), 7.05 (d, J = 0.8 Hz, 1H), 5.70 (t, J = 9.0 Hz, 1H), 4.96 (d, J = 8.9 Hz, 1H), 4.32 – 4.19 (m, 2H), 4.11 (ddd, J = 9.5, 8.3, 7.1 Hz, 1H), 4.05 (s, 3H), 4.06 – 3.96 (m, 1H), 3.94 (td, J = 8.9, 6.5 Hz, 1H), 3.81 – 3.67 (m, 2H), 3.15 (dt, J = 13.2, 8.9 Hz, 1H), 2.16 (ddd, J = 13.2, 9.0, 6.6 Hz, 1H), 0.80 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 188.9, 170.2, 155.5, 145.4, 141.9, 129.8, 129.2 (q, J = 32.3 Hz), 128.8, 127.2, 125.1 (q, J = 3.7 Hz), 124.2

(q, $J = 272.0$), 67.4, 66.1, 62.4, 60.5, 46.4, 44.2, 36.1, 35.5, 13.6. ^{19}F NMR (377 MHz, Chloroform- d) δ -62.6. M.p. 175.1–177.6 °C. HRMS (ESI) calculated for $[\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_4\text{O}_5]^+$ $\{M^+H^+\}$ requires 481.1693, found 481.1694.

Ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)pyrrolidine-2-carboxylate (17)

Reaction was carried out with the general procedure with (2-(3,5-bis(trifluoromethyl)phenyl)cyclopropyl)(1-methyl-1H-imidazol-2-yl)methanone (147.1 mg, 0.41 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), $\text{Yb}(\text{OTf})_3$ (248.0 mg, 0.40 mmol), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 14 hours giving the crude product as a yellow oil (9:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/ NEt_3 then 2:3 acetone/pentanes) to give the pure product as a white solid (174.0 mg, 0.32 mmol, 78 % yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.85 (d, $J = 1.5$ Hz, 2H), 7.74 – 7.69 (m, 1H), 7.15 (d, $J = 0.9$ Hz, 1H), 7.05 (d, $J = 0.9$ Hz, 1H), 5.68 (dd, $J = 9.5, 8.1$ Hz, 1H), 5.00 (d, $J = 8.3$ Hz, 1H), 4.33 – 4.19 (m, 2H), 4.09 (ddd, $J = 9.4, 8.4, 7.1$ Hz, 1H), 4.04 (s, 3H), 4.02 – 3.92 (m, 2H), 3.84 – 3.70 (m, 2H), 3.21 (ddd, $J = 13.4, 9.5, 8.7$ Hz, 1H), 2.17 (ddd, $J = 13.8, 8.2, 5.7$ Hz, 1H), 0.84 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 188.6, 169.7, 155.6, 143.7, 141.8, 131.4 (q, $J = 33.2$ Hz), 129.8, 128.9 (q, $J = 3.8$ Hz), 127.2, 123.3 (q, $J = 272.8$ Hz), 120.9 (sept, $J = 7.6$ Hz), 67.3, 65.8, 62.4, 60.7, 46.5, 44.3, 36.0, 35.0, 13.5. ^{19}F NMR (377 MHz, Chloroform- d) δ -62.9. M.p. 159.8 – 161.4 °C. HRMS (ESI) calculated for $[\text{C}_{23}\text{H}_{23}\text{F}_6\text{N}_4\text{O}_5]^+$ $\{M^+H^+\}$ requires 549.1567, found 549.1570.

Ethyl 3-(4-bromophenyl)-5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)pyrrolidine-2-carboxylate (18)

Reaction was carried out with the general procedure with (2-(4-bromophenyl)cyclopropyl)(1-methyl-1H-imidazol-2-yl)methanone (123.4 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), $\text{Yb}(\text{OTf})_3$ (248.0 mg, 0.40 mmol), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 8 hours giving the crude product as a yellow oil (5:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/ NEt_3 then 2:3 acetone/pentanes) to give the pure product as a white solid (159 mg, 0.32 mmol, 85 % yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.37 (d, $J = 8.5$ Hz, 2H), 7.19 (d, $J = 8.5$ Hz, 2H), 7.14 (d, $J = 0.9$ Hz, 1H), 7.04 (d, $J = 0.9$ Hz, 1H), 5.67 (t, $J = 9.0$ Hz, 1H), 4.91 (d, $J = 8.9$ Hz, 1H), 4.31 – 4.19 (m, 2H), 4.9 (ddd, $J = 9.4, 8.3, 7.1$ Hz, 1H), 4.04 (s, 3H), 4.00 (ddd, $J = 9.3, 8.3, 6.8$ Hz, 1H), 3.84 (td, $J = 9.0, 6.8$ Hz, 1H), 3.81 – 3.69 (m, 2H), 3.11 (dt, $J = 13.2, 8.8$ Hz, 1H), 2.12 (ddd, $J = 13.2, 9.1, 6.7$ Hz, 1H), 0.87 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 189.0, 170.3, 155.5, 141.9, 140.2, 131.2, 130.2, 129.7, 127.1, 120.8, 67.4, 66.1, 62.3, 60.5, 46.4, 43.9, 36.0, 35.7, 13.7. M.p. 169.0–172.3 °C. HRSM (ESI) calculated for $[\text{C}_{21}\text{H}_{24}\text{BrN}_4\text{O}_5]^+$ $\{M^+H^+\}$ requires 491.0925, found 491.0925.

Ethyl 5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)-3-(o-tolyl)pyrrolidine-2-carboxylate (19)

Reaction was carried out with the general procedure with (1-methyl-1H-imidazol-2-yl)(2-(o-tolyl)cyclopropyl)methanone (96.0 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-

yl)imino)acetate (149.0 mg, 0.8 mmol), Yb(OTf)₃ (248.0 mg, 0.40 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 12 hours giving the crude product as a yellow oil (4:1 d.r.). Product was purified by column chromatography (3:1:1 hexanes/EtOH/NEt₃) and recrystallization (acetone/pentanes liquid/liquid diffusion) to give the pure product as a white crystalline solid (128.0 mg, 0.30 mmol, 75 % yield). ¹H NMR (500 MHz, Chloroform-d) δ 7.33 – 7.30 (m, 1H), 7.14 (d, J = 0.9 Hz, 1H), 7.12 – 7.05 (m, 3H), 7.04 (d, J = 0.9 Hz, 1H), 5.69 (dd, J = 10.2, 7.4 Hz, 1H), 4.82 (d, J = 9.7 Hz, 1H), 4.35 – 4.18 (m, 3H), 4.09 – 3.95 (m, 5H), 3.69 (dq, J = 10.7, 7.1 Hz, 1H), 3.58 (dq, J = 10.7, 7.1 Hz, 1H), 2.98 (dt, J = 12.5, 7.6 Hz, 1H), 2.38 (s, 3H), 2.32 (dt, J = 12.6, 9.8 Hz, 1H), 0.74 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 189.21, 171.0, 155.7, 142.1, 138.3, 136.7, 129.8, 129.6, 127.0, 127.0, 126.7, 126.0, 67.0, 66.9, 62.2, 60.3, 46.5, 40.5, 36.1, 35.2, 19.9, 13.5. M.p. 156.9–158.6 °C. HRMS (ESI) calculated for [C₂₂H₂₇N₄O₅]⁺ {M⁺H⁺} requires 427.1976, found 427.1978.

Ethyl 5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)-3-(pyridin-3-yl)pyrrolidine-2-carboxylate (20)

Reaction was carried out with a modified version of the general procedure with (1-methyl-1H-imidazol-2-yl)(2-(pyridin-3-yl)cyclopropyl)methanone (91.0 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), Yb(OTf)₃ (149.0 mg, 0.20 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 8 hours giving the crude product as a yellow oil (5:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ then 3:1 acetone/pentanes) to give the pure product as a colorless oil in a mixture of inseparable diastereomers (62.8 mg, 0.15 mmol, 38 % yield, 6.5:1:0.5 dr). ¹H NMR (500 MHz, Chloroform-d) δ 8.47 (dd, J = 2.4, 0.8 Hz, 1H), 8.44 (dd, J = 4.8, 1.6 Hz, 1H), 7.79 (dt, J = 8.0, 1.9 Hz, 1H), 7.21 (ddd, J = 8.0, 4.7, 0.8 Hz, 1H), 7.15 (d, J = 0.9 Hz, 1H), 7.05 (d, J = 0.9 Hz, 1H), 5.70 (t, J = 9.0 Hz, 1H), 4.98 (d, J = 8.6 Hz, 1H), 4.31 – 4.19 (m, 2H), 4.15 – 4.08 (m, 1H), 4.05 (s, 3H), 3.99 (ddd, J = 9.2, 8.3, 6.9 Hz, 1H), 3.86 (td, J = 8.8, 6.0 Hz, 1H), 3.82 – 3.70 (m, 2H), 3.17 (dt, J = 13.4, 9.1 Hz, 1H), 2.13 (ddd, J = 13.3, 8.7, 6.0 Hz, 1H), 0.85 (t, J = 7.2 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 188.9, 170.0, 155.5, 149.9, 148.5, 141.9, 136.8, 135.8, 129.8, 127.2, 123.3, 67.3, 65.8, 62.4, 60.6, 46.4, 41.7, 36.1, 35.3, 13.7. HRMS (ESI) calculated for [C₂₀H₂₄N₅O₅]⁺ {M⁺H⁺} requires 414.1772, found 414.1772.

Ethyl 3-(furan-3-yl)-5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)pyrrolidine-2-carboxylate (21)

Reaction was carried out with the general procedure with (2-(furan-3-yl)cyclopropyl)(1-methyl-1H-imidazol-2-yl)methanone (86.0 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), Yb(OTf)₃ (248.0 mg, 0.40 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 8 hours giving the crude product as a yellow oil (4:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ then 2:3 acetone/pentanes) to give the product as a clear oil in a 4:1 mixture of two inseparable diastereomers (113.0 mg, 0.28 mmol, 70 % yield). Product decomposes at room temperature. Major Diastereomer: ¹H NMR (500 MHz, Chloroform-d) δ 7.31 – 7.26 (m, 2H), 7.13 (d, J = 0.9 Hz, 1H), 7.05 (d, J =

0.9 Hz, 1H), 6.39 (dd, $J = 2.0, 0.9$ Hz, 1H), 5.58 (t, $J = 8.8$ Hz, 1H), 4.76 (d, $J = 8.3$ Hz, 1H), 4.31 – 4.13 (m, 3H), 4.4 (s, 3H), 3.93 (q, $J = 7.4$ Hz, 2H), 3.81 (td, $J = 8.2, 6.5$ Hz, 1H), 3.04 (ddd, $J = 13.0, 9.2, 8.1$ Hz, 1H), 2.11 (ddd, $J = 13.0, 8.4, 6.6$ Hz, 1H), 1.03 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 189.20, 170.71, 155.60, 143.10, 142.52, 140.00, 129.59, 127.02, 124.19, 110.76, 67.35, 66.26, 62.26, 60.46, 46.38, 36.06, 35.72, 35.34, 13.82. HRMS (ESI) calculated for $[\text{C}_{19}\text{H}_{23}\text{N}_4\text{O}_6]^+ \{ \text{M}^+\text{H}^+ \}$ requires 403.1612, found 403.1609. Minor diastereomer: ^1H NMR (500 MHz, Chloroform- d) δ 7.41 – 7.40 (m, 1H), 7.37 – 7.35 (m, 1H), 7.14 (d, $J = 0.9$ Hz, 1H), 7.07 (d, $J = 0.9$ Hz, 1H), 6.58 (dd, $J = 2.0, 0.9$ Hz, 1H), 5.65 (dd, $J = 8.5, 5.8$ Hz, 1H), 4.35 (d, $J = 7.0$ Hz, 1H), 4.24 – 4.10 (m, 3H), 4.09 – 4.00 (m, 1H), 4.00 (s, 3H), 3.98 – 3.93 (m, 1H), 3.81 – 3.74 (m, 1H), 3.57 (dt, $J = 9.2, 7.1$ Hz, 1H), 2.77 (dt, $J = 12.9, 8.8$ Hz, 1H), 2.23 (ddd, $J = 13.0, 7.2, 5.8$ Hz, 1H), 1.25 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 189.4, 171.2, 156.9, 142.9, 141.8, 139.4, 129.3, 127.5, 125.8, 110.0, 68.2, 64.9, 61.7, 61.3, 43.8, 36.4, 36.1, 33.3, 14.1.

Diethyl 5-(1-methyl-*im*-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)-3-phenylpyrrolidine-2,4-dicarboxylate (22)

Reaction was carried out with the general procedure with ethyl 2-(1-methyl-1H-imidazole-2-carbonyl)-3-phenylcyclopropanecarboxylate (119.0 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (149.0 mg, 0.8 mmol), $\text{Yb}(\text{OTf})_3$ (248.0 mg, 0.40 mmol), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was stopped after 24 hours giving the crude product as a yellow oil (7:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/ NEt_3 then 2:3 acetone/pentanes) to give the product as colorless oil (73.6 mg, 0.15 mmol, 38 % yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.40 – 7.36 (m, 2H), 7.30 – 7.25 (m, 3H), 7.23 – 7.18 (m, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 5.96 (d, $J = 8.7$ Hz, 1H), 5.05 (d, $J = 9.2$ Hz, 1H), 4.25 – 4.17 (m, 1H), 4.14 – 4.00 (m, 8H), 3.78 – 3.63 (m, 2H), 3.63 – 3.53 (m, 2H), 1.09 (t, $J = 7.1$ Hz, 3H), 0.79 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 187.5, 171.5, 169.6, 155.4, 142.7, 140.0, 130.0, 128.7, 128.3, 127.6, 127.3, 67.5, 66.2, 62.0, 61.2, 60.5, 52.0, 47.3, 36.0, 29.7, 13.9, 13.56. HRMS (ESI) calculated for $[\text{C}_{24}\text{H}_{29}\text{N}_4\text{O}_7]^+ \{ \text{M}^+\text{H}^+ \}$ requires 485.2031, found 485.2032.

Diethyl 5-(1-methyl-*im*-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)pyrrolidine-2,3-dicarboxylate (23)

Reaction was carried out with a modified version of the general procedure with ethyl 2-(1-methyl-1H-imidazole-2-carbonyl)cyclopropanecarboxylate (89.0 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (372.0 mg, 2.0 mmol), $\text{Sc}(\text{OTf})_3$ (98.0 mg, 0.20 mmol), $\text{Ir}(\text{4-CF}_3\text{-ppy})_3$ (3.4 mg, 0.004 mmol), and MeCN (4 mL). The reaction was complete after 20 hours giving the crude product as a yellow oil (1.2:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/ NEt_3 then 2:3 acetone/pentanes) to give the pure product in a 1.2:1 ratio of separable diastereomers (83.0 mg, 0.20 mmol, 51 % yield). ^1H NMR (500 MHz, Chloroform- d) δ 7.12 (d, $J = 0.9$ Hz, 1H), 7.06 (d, $J = 0.9$ Hz, 1H), 5.53 (dd, $J = 9.3, 2.3$ Hz, 1H), 4.46 (d, $J = 7.8$ Hz, 1H), 4.23 – 4.09 (m, 7H), 3.98 (s, 3H), 3.67 – 3.59 (m, 2H), 2.69 (ddd, $J = 12.8, 11.0, 9.3$ Hz, 1H), 2.48 (ddd, $J = 12.8, 8.4, 2.3$ Hz, 1H), 1.33 – 1.19 (m, 6H). ^{13}C NMR (126 MHz, Chloroform- d) δ 188.70, 171.14, 171.05, 157.14, 143.14, 129.37, 127.69, 64.24, 61.70, 61.24, 61.02, 60.00, 43.86,

41.93, 35.99, 27.87, 14.10, 14.05. HRMS (ESI) calculated for $[C_{18}H_{25}N_4O_7]^+ \{M^+H^+\}$ requires 409.1718, found 409.1719. Minor diastereomer: Colorless oil. 1H NMR (500 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 0.9 Hz, 1H), 7.04 (d, *J* = 0.9 Hz, 1H), 5.44 (dd, *J* = 8.7, 7.9 Hz, 1H), 4.55 (d, *J* = 8.3 Hz, 1H), 4.28 (ddd, *J* = 9.4, 8.6, 6.1 Hz, 1H), 4.25 – 4.15 (m, 3H), 4.15 – 4.08 (m, 2H), 4.02 – 3.94 (m, 4H), 3.79 (ddd, *J* = 9.2, 8.3, 6.1 Hz, 1H), 3.64 (q, *J* = 8.2 Hz, 1H), 2.93 (dt, *J* = 12.8, 7.8 Hz, 1H), 2.42 (dt, *J* = 12.8, 8.6 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 188.6, 171.0, 170.8, 155.7, 142.0, 129.6, 127.0, 67.2, 65.4, 62.2, 60.9, 60.9, 46.5, 44.5, 36.0, 31.2, 14.1, 14.1. HRMS (ESI) calculated for $[C_{18}H_{25}N_4O_7]^+ \{M^+H^+\}$ requires 409.1718, found 409.1718.

Ethyl 1-(2-oxooxazolidin-3-yl)-3-phenyl-5-picolinoylpyrrolidine-2-carboxylate (24)

Reaction was carried out with a modified version of the general procedure with (2-phenylcyclopropyl)(pyridin-2-yl)methanone (89.4 mg, 0.40 mmol), (*E*)-ethyl 2-((2-oxooxazolidin-3-yl)imino)acetate (224.0 mg, 1.20 mmol), Sc(OTf)₃ (99.0 mg, 0.20 mmol, 0.5 equiv.), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 8 hours giving the crude product as a yellow oil (20:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ then 1:3 acetone/pentanes) to give the pure product as a colorless oil in a 20:1 mixture of two inseparable diastereomers (65.6 mg, 0.16 mmol, 40 % yield). Product decomposes slowly at room temperature. 1H NMR (500 MHz, Chloroform-*d*) δ 8.65 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.12 (m, 1H), 5.89 (t, *J* = 9.1 Hz, 1H), 4.96 (d, *J* = 9.1 Hz, 1H), 4.32 – 4.20 (m, 2H), 4.19 – 4.11 (m, 2H), 3.89 (td, *J* = 9.0, 6.7 Hz, 1H), 3.79 – 3.65 (m, 2H), 3.18 (dt, *J* = 13.1, 8.9 Hz, 1H), 2.06 (ddd, *J* = 13.1, 9.5, 6.8 Hz, 1H), 0.81 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.2, 170.5, 155.6, 152.5, 149.1, 141.2, 136.8, 128.4, 128.1, 127.4, 126.9, 122.3, 67.4, 66.0, 62.5, 60.3, 46.5, 44.5, 35.5, 13.6. HRMS (ESI) calculated for $[C_{22}H_{24}N_3O_5]^+ \{M^+H^+\}$ requires 410.1711, found 410.1707.

3-(2-(1-Methyl-1H-imidazole-2-carbonyl)-4-phenylpyrrolidin-1-yl)oxazolidin-2-one (25)

Reaction was carried out with the general procedure with (1-methyl-1H-imidazol-2-yl)(2-phenylcyclopropyl)methanone (91.0 mg, 0.40 mmol), 3-(methyleamino)oxazolidin-2-one (91.0 mg, 0.8 mmol), Yb(OTf)₃ (248.0 mg, 0.40 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was complete after 12 hours giving the crude product as a yellow oil (5:1 d.r.). Product was purified twice by column chromatography (3:1:1 hexanes/EtOH/NEt₃ and 9:1 EtOAc/pentanes) and to give the product in a 13:1 mixture of diastereomers as a white solid (95.0 mg, 0.28 mmol, 70 % yield). 1H NMR (500 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 4H), 7.23 – 7.17 (m, 1H), 7.14 (d, *J* = 0.9 Hz, 1H), 7.04 (d, *J* = 0.9 Hz, 1H), 5.59 (dd, *J* = 10.6, 6.7 Hz, 1H), 4.33 – 4.20 (m, 2H), 4.03 (s, 3H), 3.89 – 3.72 (m, 4H), 3.48 (dd, *J* = 9.0, 7.4 Hz, 1H), 2.92 (dt, *J* = 12.0, 6.8 Hz, 1H), 2.08 (dt, *J* = 12.6, 10.3 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 190.1, 155.9, 142.8, 142.4, 129.5, 128.5, 127.3, 127.1, 126.6, 67.6, 61.6, 58.3, 44.7, 42.5, 38.2, 36.1. HRMS (ESI) calculated for $[C_{18}H_{21}N_4O_3]^+ \{M^+H^+\}$ requires 341.1608, found 341.1606.

Ethyl 2-methyl-5-(1-methyl-1H-imidazole-2-carbonyl)-1-(2-oxooxazolidin-3-yl)-3-phenylpyrrolidine-2-carboxylate (26)

Reaction was carried out with the general procedure with (1-methyl-1H-imidazol-2-yl)(2-(pyridin-3-yl)cyclopropyl)methanone (91.0 mg, 0.40 mmol), ethyl 2-((2-oxooxazolidin-3-yl)imino)propanoate (160.0 mg, 0.8 mmol), Yb(OTf)₃ (248.0 mg, 0.40 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and THF (4 mL). The reaction was quenched after 72 hours giving the crude product as a yellow oil (>10:1 d.r.). Product was purified twice by column chromatography (8:1:1 hexanes/EtOH/NEt₃ then 2:1 acetone/pentanes) to give the product as a colorless oil with minor impurities (52.9 mg, 0.12 mmol, 31 % yield, >10:1 dr; 65 % RSM). ¹H NMR (500 MHz, Chloroform-d) δ 7.26 – 7.17 (m, 5H), 7.13 (d, J = 0.9 Hz, 1H), 7.02 (d, J = 0.9 Hz, 1H), 6.0 (dd, J = 9.7, 7.6 Hz, 1H), 4.30 – 4.24 (m, 2H), 4.10 (q, J = 8.9 Hz, 1H), 4.4 (s, 3H), 3.89 – 3.82 (m, 1H), 3.80 – 3.73 (m, 1H), 3.72 – 3.64 (m, 1H), 3.52 (dd, J = 10.5, 7.3 Hz, 1H), 2.96 (dt, J = 12.4, 7.4 Hz, 1H), 2.48 (q, J = 10.4 Hz, 1H), 1.64 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 189.9, 173.2, 157.0, 142.0, 139.0, 129.5, 128.3, 128.1, 127.2, 126.8, 73.7, 64.4, 62.0, 60.5, 54.0, 47.3, 36.1, 33.4, 20.2, 13.6. HRMS (ESI) calculated for [C₂₂H₂₆N₅O₅]⁺ {M⁺H⁺} requires 427.1976, found 427.1976.

1-(Benzyloxy)-5-methyl-4-phenylpyrrolidin-2-yl(1-methyl-1H-imidazol-2-yl)methanone (27)

Reaction was carried out with a modified version of the general procedure with (1-methyl-1H-imidazol-2-yl)(2-phenylcyclopropyl)methanone (91.0 mg, 0.40 mmol), (*E*)-acetaldehyde O-benzyl oxime (298.0 mg, 2.0 mmol), Sc(OTf)₃ (98.0 mg, 0.20 mmol), Ir(4-CF₃-ppy)₃ (3.4 mg, 0.004 mmol), and CH₂Cl₂ (4 mL). The reaction of irradiated with a 8 W blue LED strip. The reaction was stopped after 72 hours giving the crude product as a yellow oil (10:1 d.r.). Product was purified by column chromatography (1:4 acetone/pentanes) to give the product as a colorless oil as an inseparable mixture of two diastereomers (90.2 mg, 0.24 mmol, 60 % yield, 10:1 dr). ¹H NMR (500 MHz, Chloroform-d) δ 7.54 (d, J = 7.0 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.33 – 7.19 (m, 4H), 7.6 – 7.00 (m, 3H), 4.51 (d, J = 10.2 Hz, 1H), 4.25 (d, J = 10.2 Hz, 1H), 4.16 – 4.04 (m, 2H), 4.01 (s, 3H), 3.42 (dq, J = 9.3, 6.1 Hz, 1H), 2.33 – 2.20 (m, 2H), 1.33 (d, J = 6.1 Hz, 3H). ¹³C NMR (126 MHz, Chloroform-d) δ 193.0, 142.9, 141.8, 137.2, 129.4, 128.8, 128.4, 128.2, 128.1, 127.7, 127.5, 127.4, 77.3, 71.0, 65.3, 48.2, 36.3, 34.3, 18.3. HRMS (ESI) calculated for [C₂₃H₂₆N₃O₆]⁺ {M⁺H⁺} requires 376.2020, found 376.2016.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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■ **Azomethine ylide cycloadditions (e.g., Grigg)**

■ **Donor-acceptor cyclopropane cycloadditions (e.g., Kerr)**

■ **Photoredox [3+2] cycloadditions? (this work)**

Figure 1.
Cycloaddition routes to pyrrolidine rings.

Figure 2.

Experiments probing the scope of photocatalytic [3+2] cycloaddition. Unless otherwise noted, reactions were conducted using 1 equiv of cyclopropane, 2 equiv of hydrazone, 1 equiv of Yb(OTf)₃, and 0.01 equiv of Ir(4-CF₃-ppy)₃, in THF, and were irradiated with a blue LED. ^aReaction carried out with 0.3 equiv. Yb(OTf)₃. ^bReaction carried out with 0.5 equiv. Yb(OTf)₃. ^cReaction carried out with 5 equiv. of coupling partner and 0.5 equiv. of Sc(OTf)₃ instead of Yb(OTf)₃.

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Table 1.Examination of (hetero)aryl ketones for photoredox [3+2] cycloadditions^a

entry	ketone	$E_{p/2}$ w/o Sc(OTf) ₃	$E_{p/2}$ with Sc(OTf) ₃	$E_{p/2}$	yield (dr)
1	1	-1.88 V	-1.02 V	0.86 V	0% (--)
2	7	-1.95 V	-0.85 V	1.10 V	88% (2:1)
3	8	-1.70 V	-0.50 V	1.20 V	70% (1:1)

^a All potentials referenced to SCE.^b Yields and diastereomer ratios determined by ¹H NMR analysis.

Table 2.Examination of (hetero)aryl ketones for photoredox [3+2] cycloadditions^a

entry	photocatalyst	$E_0 (M^{n+1}/M^{n*})$	$E_0 (M^{n+1}/M^n)$	yield ^b
1	Ru(bpy) ₃ (PF ₆) ₂	-0.81 V	+ 1.29 V	0%
2	Ir(dF(CF ₃)ppy) ₂ dtbbpyPF ₆	-0.86 V	+ 1.72 V	8%
3	Ir(dF(<i>t</i> -Bu)ppy) ₂ (dtbbpy)PF ₆	-0.86 V	+ 1.54 V	14%
4	Ir(Fppy) ₂ (dtbbpy)PF ₆	-0.90 V	+ 1.40 V	20%
5	Ir(ppy) ₂ (dtbbpy)PF ₆	-0.98 V	+ 1.23 V	28%
6	Ir(ppy) ₂ (dMeObpy)PF ₆	-1.00 V	+ 1.21 V	32%
7	Ir(dtbbpy) ₂ (dtbbpy)PF ₆	-1.04 V	+ 1.13 V	37%
8	Ir(4-CF ₃ ppy) ₃	-1.41 V	+ 1.04 V	53%
9	Ir(dFppy) ₃	-1.62 V	+0.98 V	50%
10	Ir(3- <i>t</i> Buppy) ₃	-1.66 V	+0.70 V	9%
11	Ir(ppy) ₃	-1.67 V	+0.72 V	8%

^aAll potentials referenced to SCE.^bYields and diastereomer ratios determined by ¹H NMR analysis.

Table 3.

Optimization studies for photocatalytic [3+2] synthesis of pyrrolidines.

entry	change from optimal conditions	yield ^a	dr
1	none	85% ^b	5:1
2 ^c	1.1 equiv. 12	75%	3.4:1
3 ^d	1.1 equiv. 12	51%	3.4:1
4 ^d	1.1 equiv. 12 , no MgSO ₄	46%	3:1
5 ^d	1.1 equiv. 12 , 0.5 equiv Yb(OTf) ₃ , no MgSO ₄	47%	2.5:1
6 ^d	1.1 equiv. 12 , 0.5 equiv Yb(OTf) ₃ , CH ₂ Cl ₂ , no MgSO ₄	56%	2:1
7 ^d	1.1 equiv. 12 , 0.5 equiv Sc(OTf) ₃ , CH ₂ Cl ₂ , no MgSO ₄	62%	1:1
8 ^d	1.1 equiv. 12 , 0.1 equiv Yb(OTf) ₃	45%	2.5:1

^aYields determined by ¹H NMR analysis unless otherwise noted.^bIsolated yield.^c3 h reaction time.^dUsing an 18 W white LED, 5 h reaction time.