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The Photochemical Rearrangement of Chiral Oxaziridines in Continuous Flow. Application Toward the Scale-Up of a Chiral Bicyclic Lactam.

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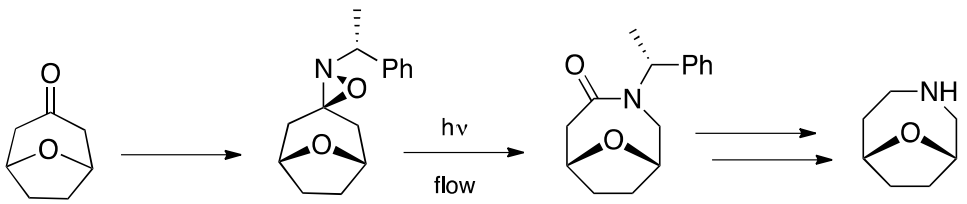


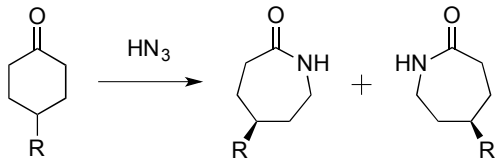
ABSTRACT: A method for synthesizing chiral lactams from chiral oxaziridines in continuous flow is described. The oxaziridines are readily available from cyclic ketones. Photolysis of the oxaziridines using the Booker-Milburn flow system provides conversion to the chiral lactams in good yield and short residence times. Application of this chemistry toward the synthesis of a chiral bicyclic lactam is described.

Keywords: oxaziridine, photolysis, continuous flow, bicyclic

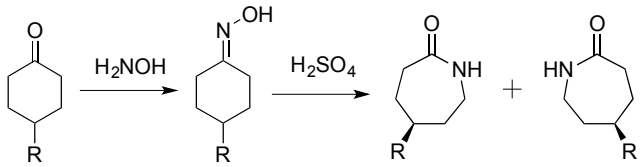
INTRODUCTION

The conversion of cyclic ketones to ring-expanded lactams can be readily accomplished using the Schmidt[1], or Beckmann[2] rearrangements. On prochiral substrates however, the lack of directional control over the nitrogen insertion affords both enantiomers of the product (Scheme 1).

Schmidt Reaction



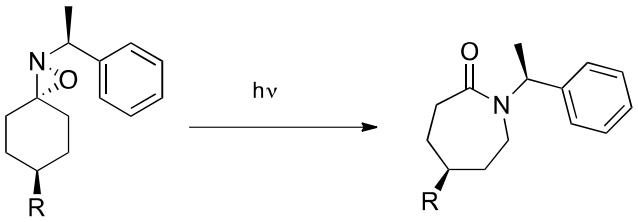
Beckmann rearrangement



Scheme 1. Schmidt & Beckmann rearrangements of prochiral ketones.

An interesting variant originally reported by Lattes[3] and studied extensively by Aubé[4], involves a two-step sequence in which prochiral ketones are converted to chiral oxaziridines that undergo a stereoselective photolytic rearrangement to produce the lactam as a single diastereomer (Scheme 2).

Lattes-Aubé Reaction



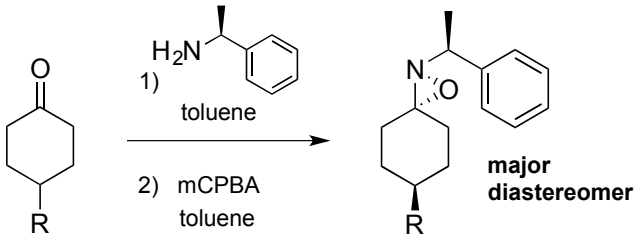
Scheme 2. Photochemical conversion of spiro-oxaziridines to lactams.

The drawback to this method is the use of photolysis, a technique not commonly practiced by most chemists, due in part to scale-limitations. Light penetration in a UV reactor falls off rapidly with increasing distance from the lamp leading to non-uniform irradiation of the reaction mixture on a larger scale. This inefficiency can lead to long reaction times and product decomposition from over-irradiation.[5] A solution to this problem, first proposed years ago[6], is to pump a solution of substrate through UV-transparent tubing that is wrapped around the quartz immersion well of a typical UV reactor. The narrow diameter of the tubing leads to uniform irradiation of the reaction. The Booker-Milburn group demonstrated the utility of this concept for scale-up by performing 2+2 and 5+2 cycloadditions in flow at a rate that could produce tens of grams of product per day.[7] They improved the efficiency of the original design by triple-wrapping the tubing around the UV reactor to maximize absorption of the photons generated. The Seeberger group has used a similar setup to produce the anti-malarial drug, artemisinin, in 200 g quantities per day.[8] Several other groups have also reported good results when performing photochemistry in continuous flow using wrapped reactors.[9]

Recently, we needed to convert a prochiral bicyclic ketone to a chiral bicyclic lactam as part of our internal medicinal chemistry effort. The oxaziridine chemistry looked like an attractive method for accomplishing this transformation although bicyclic ring systems are essentially unknown as substrates for the Lattes-Aubé reaction.[10] We were particularly interested in performing the chemistry in continuous flow as this would allow it to be easily scaled upon success. To test the feasibility of this approach, our plan was to synthesize several known oxaziridines derived from prochiral monocyclic ketones and subject them to photolysis in a wrapped UV reactor.

SETUP & OPTIMIZATION

Several known oxaziridines[4a,4e] were synthesized using the conditions in Scheme 3. The cyclohexanones formed the corresponding imines when refluxed with (*S*)-α-methylbenzylamine in toluene with azeotropic removal of water using a Dean-Stark apparatus. The diastereomeric imines formed were not isolated but added as a toluene solution to a suspension of *m*CPBA in toluene at -78°C to form the oxaziridines in diastereomeric ratios ranging from 1:1 to 6:1.



Scheme 3. Synthesis of oxaziridines.

We assembled the simple flow chemistry setup shown in Figure 1 that was based on the

Booker-Milburn research.[7] The photochemical flow system consisted of the following components[11]: a Syrris FRX HPLC pump (red module), a medium-pressure 450 watt mercury vapor lamp, a quartz immersion well, a power source (blue module) and fluorinated ethylene propylene (FEP) tubing wrapped around the immersion well. The tubing and immersion well for the lamp were wrapped with aluminum foil (not shown in picture) to avoid UV exposure.

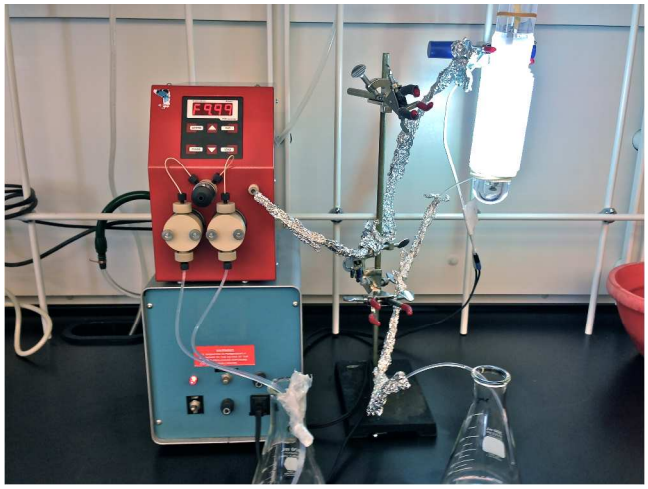


Figure 1. Flow photochemistry reaction setup.

With the oxaziridines in hand and the photochemical flow system assembled, we initially explored the oxaziridine derived from 4-*t*-Bu-cyclohexanone, as this was readily isolated as a solid. This made it possible to cleanly isolate the major diastereomer by recrystallizing the 5:1 mixture obtained in the oxidation. The relative stereochemistry of this diastereomer was confirmed through X-ray crystallography (Figure 2).

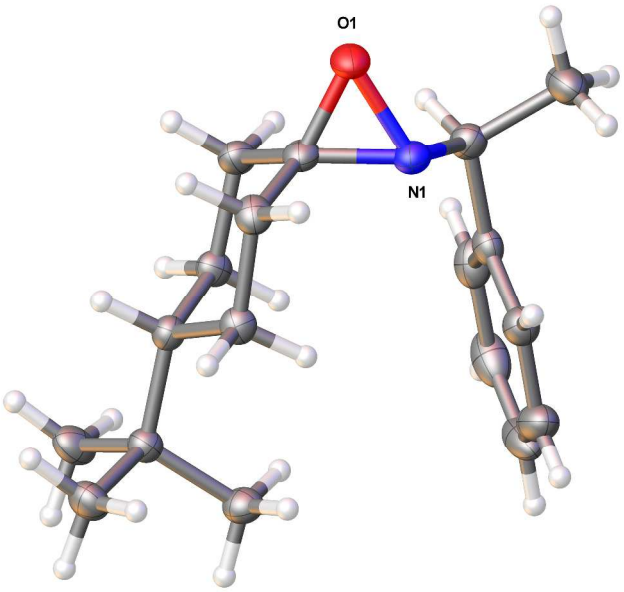


Figure 2. Oxaziridine diastereomer **3** from 4-*t*-Bu-cyclohexanone and (*S*)-α-methylbenzylamine.

We proceeded to optimize several photolysis parameters such as the solvent choice, temperature, UV filters, concentration, flow rate, and residence time. Aubé reported the best results were obtained in cyclohexane and acetonitrile.[4a] We found that performing the reaction in cyclohexane led to various levels of decomposition of both the compound and the tubing depending on the reaction conditions. The decomposition products precipitated in the lines as an orange-brown solid that blocked the transmittance of UV light leading to reduced yields of product. Changing the solvent to acetonitrile minimized the decomposition.

Initially, water was run through the immersion well to cool the reaction but this proved to be insufficient. The high temperatures that resulted led to substantial decomposition of both the substrate and eventually the tubing. Since we were not running the system under backpressure regulation, the higher temperatures led to gas bubbles in the lines caused by solvent vaporizing.

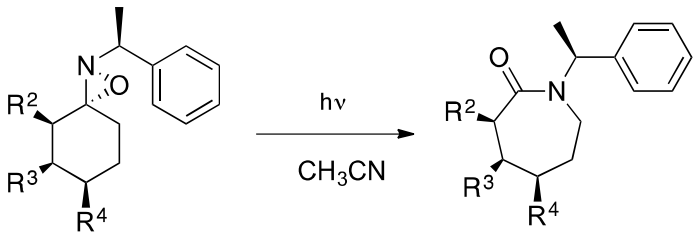
While a commercial chiller would have sufficed for solving this problem, a simple, inexpensive solution was to augment the water-cooling with a stream of cooled nitrogen running into a Dewar flask that surrounded the immersion well.[11] The Dewar flask had the added advantage of blocking extraneous UV light. The flow of nitrogen was maintained at a rate that easily kept the outside of the reactor at room temperature.

When investigating wavelength, a Vycor filter (ca. 220 nm UV cutoff) around the lamp resulted in a significantly slower reaction than when using the full UV spectrum. After investigating several concentrations and residence times, the best results were obtained with more dilute solutions (0.1M) and by triple-wrapping the reactor in FEP tubing to maximize exposure of the substrate to the UV light.[7] It should be noted that during our exploration of the system, we successfully ran very concentrated solutions and very high flow rates through this system that in theory equaled 7 kg/day of oxaziridine! However, the yields suffered somewhat during these runs, partially due to decomposition that precipitated in the tubing, so we elected to use more dilute solutions of oxaziridine.

RESULTS AND DISCUSSION

At this point, the level of optimization was sufficient to explore the photolytic conversion of the remaining oxaziridines that we had made to their corresponding lactams. Table 1 summarizes the data and compares the product yields from our flow experiments to the yields reported in batch by Aubé. As can be seen from the data, the yields for the 3- and 4-substituted cyclohexyl systems (oxaziridines 1-8) are comparable if not better than the previously reported results in batch. Substitution at the 2-position of the cyclohexyl system led to reduced yields of

the corresponding lactam although the yield was improved over the reported batch results. What is most striking is the greatly reduced time required to perform the reaction in continuous flow.



Oxaziridine	R_2	R_3	R_4	Isomer ratio	Flow % yield[a]	Batch % yield & time (hr)[4a]
1	H	H	Me	4:1	83	77 (4)
2	H	H	Et	5:1	77	76 (7)
3	H	H	*t*-Bu (*S*)	pure	82	70 (6)
4	H	H	Ph	5:1	81	87 (2)
5	H	H	OBn	3:1	72	74 (5)
6	H	H	CO_2Et	1:1	63	80 (9.5)
7	H	H	*t*-Bu (*R*)	pure	74	70 (6)
8	H	Me	H	5:1	72	78
9	OMe	H	H	6:1	54	50
10	Me	H	H	4:3	76	57

[a] 0.1M in MeCN @ 5 mL/min flow rate; tubing volume = 130 mL; residence time = 26 min; 1 g scale; isolated yields are reported.

Table 1. Results for the photolytic conversion of oxaziridines to lactams.

In our hands, the same scale reaction that reportedly took several hours in batch, took less than 30 minutes in our flow system. This is probably due in part to using the full UV spectrum rather than the specific wavelength of 254 nm used by Aubé. To demonstrate the potential of this system for scale-up, we ran oxaziridine **3** (R = *t*-Bu) through the system on a 20 g scale obtaining the desired lactam in >80% yield.

The X-ray structure of the lactam diastereomer obtained from the photolytic rearrangement of **3** was consistent with the expected structure and with the results previously reported (Figure 3).[4a]

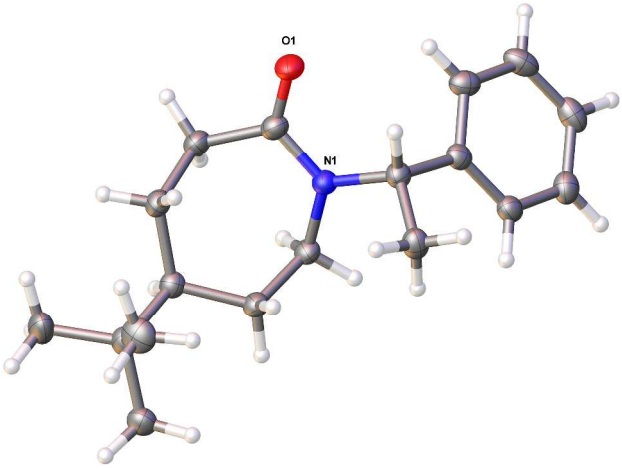
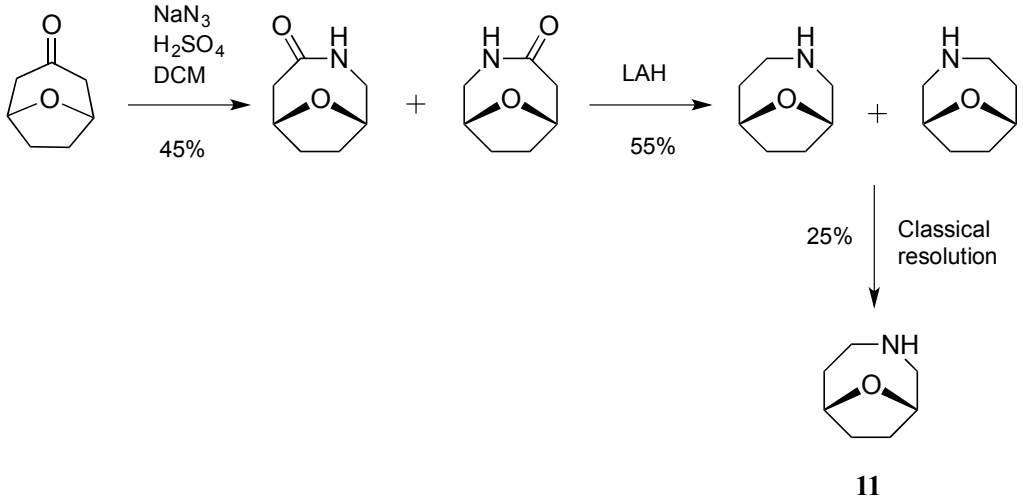


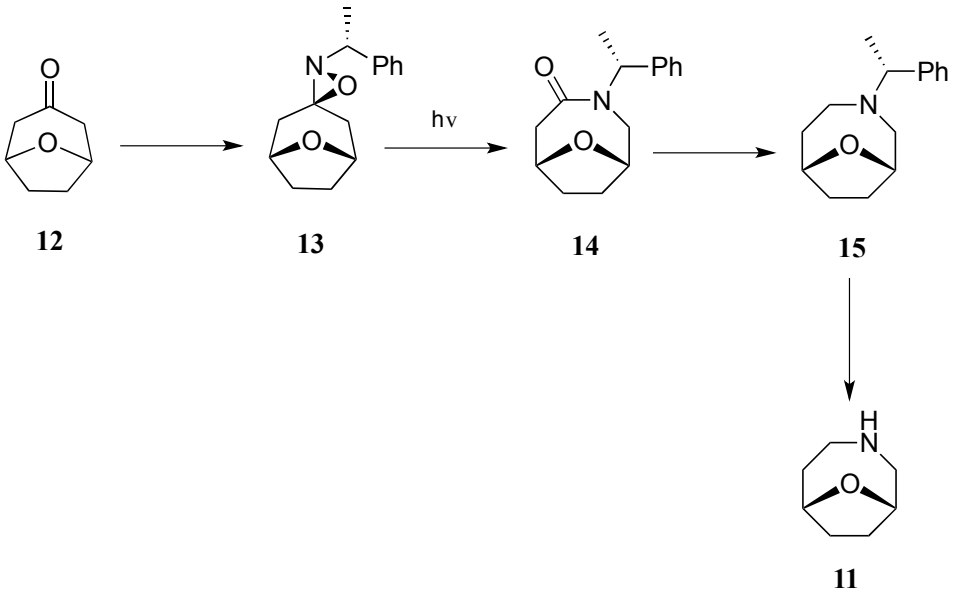
Figure 3. Lactam diastereomer from the photolysis of the *t*-Bu oxaziridine **3**.

After successfully demonstrating that the Lattes-Aubé reaction could be run in continuous flow, we turned our attention to the transformation of interest. The original route to the chiral amine **11** (Scheme 4) suffered from low yields including the classical resolution that was required in the end. Also, the generation of hydrazoic acid in the first step was a potential safety hazard that we wanted to avoid. The lack of a strong chromophore in each step presented an additional challenge.



Scheme 4. Original route for the preparation of chiral bicyclic lactam **11**.

We proposed a short, four-step asymmetric route to **11** (Scheme 5) using the Lattes-Aubé chemistry. The plan was to convert the ketone to a chiral oxaziridine in analogous fashion to the monocyclic ketones explored earlier. We postulated that (*R*)-α-methylbenzylamine was needed to form the oxaziridine that would give lactam **13** after photolysis.[12] Reduction of the lactam followed by removal of the benzyl group would afford **11**. This route provided the additional advantages of having a strong chromophore at each step and it avoided the dangerous hydrazoic acid used in the original route.



Scheme 5. Proposed synthesis of chiral bicyclic lactam **11**.

The commercially available bicyclic ketone **12** was converted to the corresponding oxaziridine **13** (Figure 4) in 51% yield as a single diastereomer. Photolysis of 80 g of **13** as a 0.1M solution in CH_3CN proceeded at a slower rate than the oxaziridines shown in Table 1. After one pass through the system at the same flow rate of 5 mL/min (t_R = 26 min), there was a significant amount of starting material remaining. However, this material was easily separated from the product by column chromatography to provide over 40 g of the chiral lactam **14** in 51% yield (99% yield based on recovered starting material). Borane reduction and debenzylation of **14** proceeded in 82% and 86% respectively to afford the desired chiral amine **11**. The stereochemistry of the amine was confirmed by comparing its optical rotation to an authentic sample. Due to shifting priorities, all further work toward scaling this compound in flow was abandoned. However, this method was clearly viable for making the chiral bicyclic amine on-scale with some additional optimization.

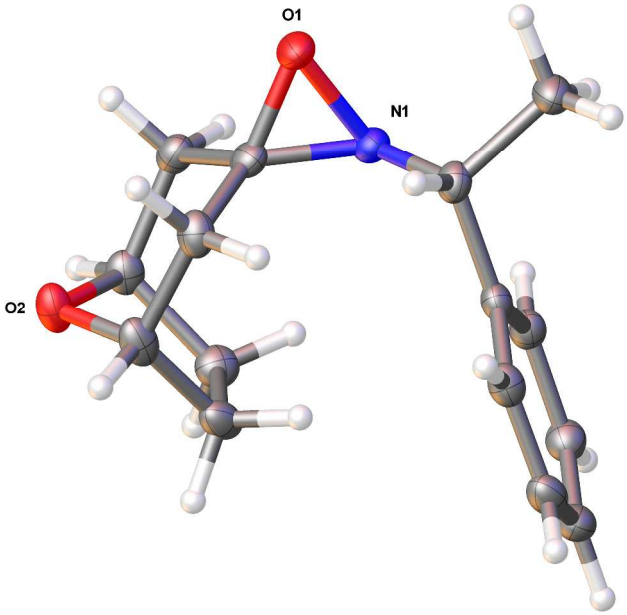


Figure 4. Oxaziridine diastereomer **13** from 8-oxabicyclo[3.2.1]octan-3-one and (*R*)-α-methylbenzylamine

In summary, we have demonstrated the Lattes-Aubé reaction in continuous flow. The yields are the same or higher than in batch and the reactions are completed in a fraction of the time. We have demonstrated the rare application of this chemistry to a bicyclic system and have shown the potential utility for performing this type of photochemical reaction on-scale.

EXPERIMENTAL SECTION

All reagents and solvents were purchased from the Aldrich Chemical company and used as obtained. The 450-watt medium-pressure UV lamp and the 290 mm immersion well were obtained from Ace Glass. Analytical thin layer chromatography (TLC) was performed on percolated silica gel 60 F254 plates and visualized with UV light (254 nm) or $KMnO_4$ stain. ^1H

NMR spectra were recorded on a 300 MHz Bruker AVANCE spectrometer. ^{1}H NMR chemical shifts are quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. ^{13}C NMR spectra were recorded at 75 MHz and chemical shifts were reported in ppm referenced to the centerline of a triplet at 77.0 ppm of $CDCl_3$ or a heptet at 39.5 ppm of DMSO-d6. LC/MS data were obtained with a Waters ACQUITY equipped with a QDa mass detector. The UPLC separations were obtained from a C18 column using an elution gradient of 5-95% CH_3CN/H_2O with 1% TFA. Optical rotations were performed on a Rudolph Autopol III polarimeter. Melting points were obtained on a Mettler-Toledo (DSC1) differential scanning calorimeter. Fluorinated ethylene propylene (FEP) tubing was purchased from E&S Technologies in Chelmsford, MA. Column chromatography was performed using SiliaSep normal phase silica (230-400 mesh) cartridges on a Teledyne ISCO Torrent purification system. The oxaziridines **1-8** in Table 1 were synthesized according to the procedures previously reported[4a] and are further exemplified in the synthesis of the oxaziridine **3** described below. Oxaziridines **9** & **10** in Table 1 were also synthesized according to previously reported procedures.[4e] All characterization data for the oxaziridines were in agreement with the previously reported values.[4a, 4e]

(1*R*,3*r*,5*S*)-2'-((*S*)-1-phenylethyl)-8-oxaspiro[bicyclo[3.2.1]octane-3,3'-[1,2]oxaziridine] (13).

A solution of 8-oxabicyclo[3.2.1]octan-3-one **(12)** (10.34 g, 81.96 mmol) and (1*R*)-1-phenylethanamine (15.6 mL, 123 mmol) in toluene (200 mL) was refluxed for 4 hours in a 500 mL RB flask equipped with a Dean Stark trap and condenser. Approximately 1.5 mL of water was collected in the trap. The imine solution was cooled to room temperature and added dropwise under nitrogen to a -78°C suspension of *m*CPBA (17.0 g, 99 mmol) in toluene (300 mL). After complete addition (~45 min), the reaction was stirred at -78°C for an additional 30 minutes. The reaction was quenched at -78°C by the addition of 1 M $Na_2S_2O_3$ (~250 mL)

followed by warm water (250 mL), and the product was extracted using 1L of Et_2O. The organic layer was washed with saturated $NaHCO_3$ solution (250 mL) followed by brine (250 mL), then concentrated to dryness and purified via silica gel chromatography (220 g ISCO column) eluting with 0-30% EtOAc in heptane over 40 minutes. Fractions containing desired product were combined and concentrated to afford 11.03 of **(13)** as a light orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 2H), 7.39 – 7.27 (m, 3H), 4.44 – 4.35 (m, 1H), 4.33 – 4.24 (m, 1H), 3.48 (q, *J* = 6.3 Hz, 1H), 2.33 (ddd, *J* = 12.9, 4.5, 3.5 Hz, 2H), 1.89 (d, *J* = 14.8 Hz, 1H), 1.71 – 1.60 (m, 1H), 1.55 (t, *J* = 4.2 Hz, 3H), 1.54 – 1.47 (m, 1H), 1.42 – 1.29 (m, 2H), 0.32 (ddd, *J* = 11.1, 6.9, 3.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 128.8, 128.1, 127.1, 82.0, 73.9, 73.3, 63.3, 43.0, 27.7, 27.6, 24.4 ppm.

General Procedure for Photolysis.

The photochemical flow reactor reported by the Booker-Milburn group was assembled by triple-wrapping 90 ft of 1/8-inch (0.095" I.D.) FEP tubing around a 290 mm quartz immersion well that housed a 450-watt medium-pressure UV lamp. The tubing was connected to a Syrris FRX HPLC pump. A 0.1M solution of the oxaziridine in CH_3CN was pumped at 5 mL/min (t_R = 26 min) through the photochemistry setup (further described in the supplementary material) and into a collection flask. The solution was evaporated and the resulting material chromatographed.

(5*S*)-5-methyl-1- [(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 1, major isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 5H), 6.05 (q, *J* = 7.1 Hz, 1H), 3.04 – 2.90 (m, 2H), 2.67 – 2.50 (m, 2H), 1.88 – 1.70 (m, 2H), 1.63 – 1.53 (m, 1H), 1.52 – 1.43 (m, 3H), 1.31 – 1.03 (m, 2H), 0.96 – 0.88 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.20, 141.04, 128.30, 127.03, 50.44, 42.75, 37.84, 36.29, 36.27, 31.51, 22.68, 16.37 ppm. LC/MS m/z 232.17.

$[\alpha]^{23.2}_{D}$ = -133.102 (c = 2.811, 281.1 mg in 10 mL MeOH).

(5*R*)-5-methyl-1- [(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 1, minor isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.23 (m, 5H), 6.05 (q, J = 7.0 Hz, 1H), 3.20 - 3.05 (m, 2H), 2.70 - 2.57 (m, 1H), 2.57 - 2.42 (m, 1H), 1.85 - 1.74 (m, 1H), 1.62 - 1.21 (m, 6H), 0.82 (t, J = 7.7 Hz, 3H), 0.62 - 0.41 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.37, 140.63, 128.28, 127.82, 127.32, 50.59, 42.00, 36.56, 36.37, 35.84, 31.28, 22.36, 15.64 ppm. LC/MS m/z 232.17. $[\alpha]^{19.8}_{D}$ = -152.574 (c = 0.68, 68 mg in 10 mL MeOH).

(5*S*)-5-ethyl-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 2, major isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.21 (m, 5H), 6.03 (q, J = 7.1 Hz, 1H), 3.09 - 2.90 (m, 2H), 2.70 - 2.46 (m, 2H), 1.94 - 1.75 (m, 2H), 1.47 (d, J = 7.3 Hz, 3H), 1.36 - 1.17 (m, 4H), 1.10 - 0.97 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.45, 141.16, 128.37, 127.16, 127.10, 50.54, 42.99, 42.86, 36.29, 35.58, 29.66, 29.27, 16.44, 11.35 ppm. LC/MS m/z 246.16. $[\alpha]^{20.1}_{D}$ = -110.371 (c = 3.58, 358 mg in 10 mL MeOH).

(5*R*)-5-ethyl-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 2, minor isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 - 7.22 (m, 5H), 6.04 (q, J = 7.0 Hz, 1H), 3.24 - 2.99 (m, 2H), 2.72 - 2.57 (m, 1H), 2.57 - 2.40 (m, 1H), 1.92 - 1.76 (m, 1H), 1.53 - 1.37 (m, 4H), 1.33 - 1.07 (m, 4H), 0.83 - 0.70 (m, 3H), 0.61 - 0.40 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.44, 140.66, 128.27, 127.81, 127.31, 50.56, 42.46, 42.03, 36.31, 34.23, 29.22, 28.93, 15.62, 11.28 ppm. LC/MS m/z 246.16. $[\alpha]^{20.4}_{D}$ = -106.931 (c=0.88, 88 mg in 10 mL MeOH).

(5*S*)-5-*t*-butyl-1- [(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 3)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.24 (m, 5H), 6.05 (q, J = 7.1 Hz, 1H), 3.20 - 2.90 (m, 2H), 2.76 - 2.62 (m, 1H), 2.60 - 2.42 (m, 1H), 2.10 - 1.85 (m, 2H), 1.58 - 1.45 (m, 3H), 1.32 - 1.05 (m, 3H), 0.91 - 0.82 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.50, 141.16, 128.38, 127.16, 127.12, 51.60, 50.50, 43.25, 36.57, 33.01, 30.61, 27.55, 24.26, 16.50 ppm. LC/MS m/z 274.2 $[\alpha]^{22.9}_{D}$ = -106.809 (c = 1.028, 102.8 mg in 10 mL MeOH). mp 96°C.

(5*S*)-5-phenyl-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 4, major isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.17 (m, 10H), 6.15 (q, J = 7.1 Hz, 1H), 3.12 (dd, J = 12.2, 8.4 Hz, 2H), 2.80 - 2.65 (m, 3H), 2.16 - 1.72 (m, 4H), 1.61 - 1.54 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.07, 146.13, 141.07, 128.66, 128.53, 127.28, 127.19, 126.73, 126.58, 50.74, 48.22, 43.16, 37.55, 36.79, 30.84, 16.63 ppm. LC/MS m/z 294.13. $[\alpha]^{19.9}_{D}$ = -49.673 (c = 1.069, 106.9 mg in 10 mL MeOH).

(5*R*)-5-phenyl-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 4, minor isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 - 7.16 (m, 8H), 7.04 (dd, J = 5.2, 3.3 Hz, 2H), 6.15 (q, J = 7.0 Hz, 1H), 3.38 - 3.18 (m, 2H), 2.85 - 2.57 (m, 3H), 2.09 - 1.94 (m, 1H), 1.84 - 1.56 (m, 2H), 1.53 (dd, J = 9.4, 4.5 Hz, 3H), 1.02 - 0.86 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.03, 146.10, 140.57, 128.53, 128.42, 127.90, 127.58, 126.62, 126.41, 50.71, 47.93, 42.40, 36.98, 35.99, 30.68, 15.61 ppm. LC/MS m/z 294.13. $[\alpha]^{20.3}_{D}$ = -141.156 (c = 0.917 , 91.7 mg in 10 mL MeOH).

(5*S*)-5-benzyloxy-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 5, major isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.23 (m, 10H), 6.08 (q, J = 7.0 Hz, 1H), 4.54 - 4.41 (m, 2H), 3.66 (d, J = 3.6 Hz, 1H), 3.47 - 3.34 (m, 1H), 2.97 (dd, J = 19.0, 7.5 Hz, 1H), 2.90 - 2.78

(m, 1H), 2.40 (ddd, J = 14.2, 8.4, 2.0 Hz, 1H), 2.05 - 1.86 (m, 2H), 1.75 - 1.55 (m, 2H), 1.50 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.31, 140.76, 138.51, 128.47, 128.41, 127.60, 127.40, 127.36, 127.30, 69.99, 50.64, 37.90, 34.10, 31.16, 28.09, 16.31 ppm. LC/MS m/z 324.15. $[\alpha]^{22.8}_D$ = - 80.919 (c = 1.132, 113.2 mg in 10 mL MeOH).

(5*R*)-5-benzyloxy-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 5, minor isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.28 (m, 10H), 6.07 (q, J = 7.1 Hz, 1H), 4.48 (t, J = 8.1 Hz, 2H), 3.60 - 3.47 (m, 1H), 3.39 (dd, J = 15.3, 9.3 Hz, 1H), 2.99 - 2.80 (m, 2H), 2.46 - 2.36 (m, 1H), 2.13 - 1.87 (m, 3H), 1.54 - 1.43 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.14, 140.82, 138.53, 128.43, 127.62, 127.54, 127.43, 127.37, 70.01, 50.65, 38.03, 33.94, 31.36, 28.19, 15.87 ppm. LC/MS m/z 324.15. $[\alpha]^{22.8}_D$ = -44.908 (c = 2.82, 282 mg in 10 mL MeOH).

Ethyl (4S)-7-oxo-1-[(1S)-1-phenylethyl]azepane-4-carboxylate (Table 1, entry 6, major isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 - 7.25 (m, 5H), 6.05 (q, J = 7.1 Hz, 1H), 4.18 - 4.10 (m, 2H), 3.17 (ddd, J = 15.7, 7.1, 1.5 Hz, 1H), 3.02 (dd, J = 15.3, 9.6 Hz, 1H), 2.79 - 2.66 (m, 1H), 2.63 - 2.44 (m, 2H), 2.12 (ddt, J = 18.2, 11.7, 4.8 Hz, 1H), 1.97 - 1.76 (m, 2H), 1.68 - 1.56 (m, 1H), 1.50 (t, J = 6.3 Hz, 3H), 1.29 - 1.23 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.56, 174.34, 140.73, 128.43, 127.28, 127.22, 60.60, 50.69, 45.74, 41.58, 35.32, 31.57, 25.62, 16.22, 14.16 ppm. LC/MS m/z 290.13. $[\alpha]^{22.5}_D$ = -70.259 (c = 1.043, 104.3 mg in 10 mL MeOH).

Ethyl (4R)-7-oxo-1-[(1S)-1-phenylethyl]azepane-4-carboxylate (Table 1, entry 6, minor isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 - 7.20 (m, 5H), 5.99 (q, J = 7.0 Hz, 1H), 4.09 - 3.98 (m, 2H), 3.17 (ddd, J = 15.5, 7.6, 1.8 Hz, 1H), 3.05 (ddd, J = 23.7, 13.2, 5.3 Hz, 1H), 2.69 (ddd, J = 14.4,

9.1, 1.6 Hz, 1H), 2.56 - 2.39 (m, 2H), 2.07 - 1.94 (m, 1H), 1.89 - 1.75 (m, 1H), 1.69 - 1.57 (m, 1H), 1.43 (d, J = 7.1 Hz, 3H), 1.32 - 1.21 (m, 1H), 1.16 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.65, 174.22, 140.32, 128.42, 127.56, 127.41, 60.50, 50.75, 45.04, 41.13, 35.27, 30.88, 25.28, 15.82, 14.11 ppm. LC/MS m/z 290.08. $[\alpha]^{22.7}_D$ = -81.243 (c = 3.041, 304.1mg in 10 mL MeOH).

(5*R*)-5-*t*-butyl-1-[(1*R*)-1-phenylethyl]azepan-2-one (Table 1, entry 7)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 - 7.04 (m, 5H), 5.86 (q, J = 7.1 Hz, 1H), 2.97 - 2.71 (m, 2H), 2.48 (ddd, J = 7.7, 6.4, 3.9 Hz, 1H), 2.40 - 2.21 (m, 1H), 1.88 - 1.65 (m, 2H), 1.37 - 1.29 (m, 3H), 1.15 - 0.89 (m, 3H), 0.67 (d, J = 5.8 Hz, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.36, 141.10, 128.34, 127.09, 51.48, 50.44, 43.16, 36.50, 32.95, 30.57, 27.52, 27.44, 24.22, 16.47 ppm. LC/MS m/z 274.2. $[\alpha]^{22.6}_D$ = 102.739 (c = 1.132 , 113.2 mg in 10 mL MeOH).

(4*R*)-4-methyl-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 8, major isomer)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.23 (m, 5H), 6.08 (q, J = 7.1 Hz, 1H), 3.15 - 3.02 (m, 2H), 2.62 - 2.42 (m, 2H), 1.85 (tdd, J = 9.6, 7.4, 2.3 Hz, 1H), 1.76 - 1.63 (m, 1H), 1.55 - 1.36 (m, 4H), 1.26 (ddd, J = 9.6, 6.4, 2.7 Hz, 1H), 1.09 - 0.90 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.55, 141.18, 128.39, 127.11, 50.57, 50.45, 38.76, 37.31, 35.25, 23.38, 20.51, 16.59 ppm. LC/MS m/z 232.17. $[\alpha]^{23.0}_D$ = - 184.170 (c = 1.012, 101.2 mg in 10 mL MeOH).

(6*R*)-6-methyl-1-[(1*S*)-1-phenylethyl]azepan-2-one (Table 1, entry 15)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 - 7.22 (m, 5H), 6.06 (q, J = 7.1 Hz, 1H), 2.93 - 2.69 (m, 2H), 2.67 - 2.46 (m, 2H), 1.88 (ddd, J = 19.4, 14.2, 7.4 Hz, 2H), 1.68 - 1.45 (m, 5H), 1.20 - 1.09 (m, 1H), 0.84 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.27, 140.83, 128.30,

127.70, 127.27, 50.55, 44.98, 43.24, 38.12, 29.09, 27.29, 22.38, 15.77 ppm. LC/MS m/z 232.17. $[\alpha]^{23.2}_{D}$ = - 156.957 (c = 0.999, 99.9 mg in 10 mL MeOH).

(1*S*,6*R*)-3-((*S*)-1-phenylethyl)-9-oxa-3-azabicyclo[4.2.1]nonan-4-one (14)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dddd, *J* = 15.5, 7.3, 5.0, 1.2 Hz, 5H), 6.18 – 6.04 (m, 1H), 4.38 (tt, *J* = 9.0, 7.7 Hz, 2H), 3.14 (d, *J* = 15.7 Hz, 1H), 2.92 – 2.75 (m, 3H), 2.11 – 1.82 (m, 4H), 1.50 (d, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.59, 140.25, 128.53, 127.37, 127.21, 75.61, 72.25, 51.03, 50.50, 50.44, 47.88, 28.75, 26.44, 16.01 ppm. $[\alpha]^{21.8}_{D}$ = 160.2° (c = 1, 100 mg / 10 mL MeOH).

(1*S*,6*R*)-3-((*S*)-1-phenylethyl)-9-oxa-3-azabicyclo[4.2.1]nonane (15)

To a solution of (1*R*,6*S*)-4-[(1*R*)-1-phenylethyl]-9-oxa-4-azabicyclo[4.2.1]nonan-3-one **4** (29.6 g, 120.7 mmol) in THF (300 mL) under nitrogen was added dropwise BH_3-THF (240 mL of 1 M, 240 mmol) in THF. The reaction was refluxed for 5.5 hours. The reaction was cooled to room temperature and the mixture was brought to pH 1 by carefully adding 20 mL of 6N aqueous HCl over 5 minutes. The solution was stirred for 1 hour, diluted with 200 mL water, and stirred for an additional hour. The solution was brought to pH 8 with saturated aqueous $NaHCO_3$ and then extracted thrice with EtOAc. The combined organics were dried ($MgSO_4$), filtered, and evaporated in vacuo to afford 27.6 g of a light yellow oil. The material was chromatographed on a 120 g ISCO silica gel column (0-25% EtOAc/heptane) to afford 23.0 g (82%) of **5** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 5H), 4.45 (t, *J* = 8.4 Hz, 1H), 4.38 – 4.28 (m, 1H), 3.85 – 3.74 (m, 1H), 2.77 (ddd, *J* = 19.5, 8.8, 4.1 Hz, 1H), 2.58 (dd, *J* = 10.6, 3.4

Hz, 2H), 2.43 – 2.28 (m, 1H), 2.23 – 2.06 (m, 1H), 2.02 – 1.84 (m, 4H), 1.44 – 1.29 (m, 4H) ppm. $[\alpha]^{19.2}_{D} = 25.683$ (c = 0.989, 98.9 mg in 10 mL MeOH).

(1*S*,6*R*)-9-oxa-3-azabicyclo[4.2.1]nonane (11)

To a suspension of (1*R*,6*S*)-4-[(1*R*)-1-phenylethyl]-9-oxa-4-azabicyclo[4.2.1]nonane (6 g, 25.9 mmol) and 10% Pd/C (wet, Degussa-type, 2.1 g, 2.01 mmol) in EtOH (90 mL) was added HCl (7.1 mL of 4 M, 28.4 mmol) in dioxane . The reaction was shaken for three hours under 50 psi hydrogen on a Parr shaker. LCMS shows some remaining benzylamine. The reaction was shaken under 50 psi of H_2 overnight. The mixture was filtered over Celite, washed with EtOH then EtOAc, and the filtrate was concentrated to give a white solid. The product was taken up in minimal MeOH and dropped into diethyl ether while stirring vigorously. The resulting white solid was filtered and dried to give 3.86 g (86%) of **11** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 9.34 (s, 1H), 4.71 - 4.31 (m, 2H), 3.56 - 2.88 (m, 4H), 2.49 - 1.70 (m, 6H) ppm. ESI-MS found 128.0 $(M+1)^+$. $[\alpha]^{22.0}_{D} = -10.88$ (c = 0.92, 92 mg in 10 mL MeOH).

SUPPORTING INFORMATION

Continuous flow photochemical reactor setup and X-ray crystallographic information for oxaziridines **3** & **13**, and the lactam derived from **3**. This information is available free of charge via the internet at http://pubs.acs.org.

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