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Article

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Stereoselective Intermolecular [2+2] Cycloadditions of Erlenmeyer-Plöchl Azlactones using Visible Light Photoredox Catalysis

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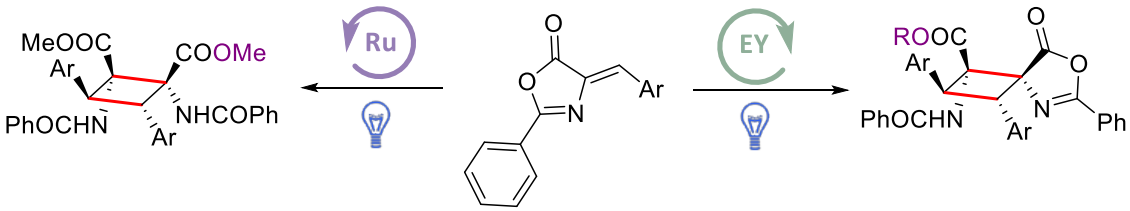
Abstract Graphic



- *Diaminotruxinic derivatives*
- *Only head-to-head coupling*
- *Regio- and diastereoselective*
- *One-pot methodology*
- *25 examples*
- *Up to 78% isolated yield*

Abstract

The first report of the preparation of symmetric and non-symmetric diaminotruxinic derivatives through the photoredox [2+2] cycloadditions of Erlenmeyer azlactones is described, affording the desired compounds in high regio- and diastereocontrol (only head-to-head coupling).

Mechanistic studies by DFT suggest that the reaction proceeds through a neutral photocatalytic pathway.

Introduction

Organic compounds containing four-membered rings are prominent structural scaffold present in a diverse family of bioactive natural products.[1,2,3] In this context, substituted cyclobutanes (specially the tetrasubstituted truxylic and truxinic acids – Figure 1) are noteworthy for their biological activities, such as antimicrobial, antibacterial and anticancer.[4,5,6,7]

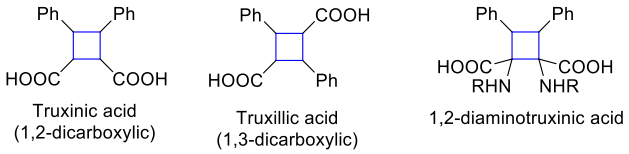


Figure 1. General structure of truxinic and truxillic acids.

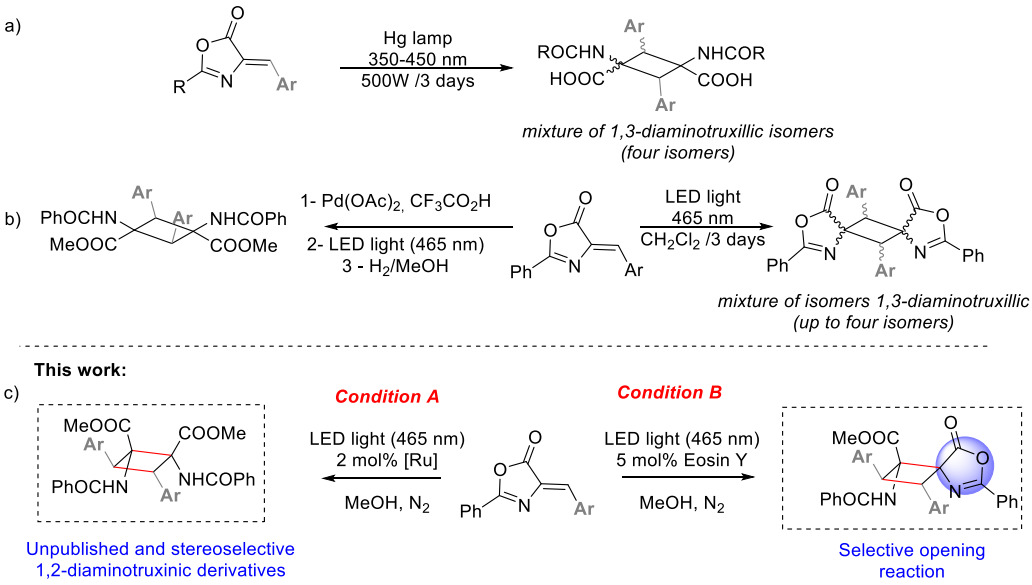
This class of compounds is generally prepared through [2+2] cycloaddition reactions. Over the last years, a powerful tool for the synthesis of cyclobutanes has been developed with the advent of photoredox catalysis.[8] Thus, the use of visible light is an interesting approach, usually tolerating the presence of sensitive functional groups, avoiding problems with decomposition by the high-energy radiation and greatly increasing the ability to achieve unique bond construction through single-electron transfer (SET) reactions, that are not possible using conventional photochemical protocols.[9]

Our research group has been recently studying the reactivity of oxazolone rings[10-14]. Thus, we envisioned that Erlenmeyer–Plöchl azlactones could be a promising substrate in [2+2] photocycloaddition, since alkenes bearing an α,β-unsaturated carbonyl group are generally easily photoexcited[8]. The head-to-tail coupling of these substrates had been previously reported in the literature, affording a 1,3-diaminotruxilic acid derivatives by either strong light irradiation (Hg lamp/ 500W) (Scheme 1a)[15] or by irradiation with low-power LEDs (Scheme 1b).[16] In both cases, a mixture of up to four isomers were obtained. Furthermore, these cyclobutane derivatives were also stereoselectively accessed in a three steps synthesis, by a combination of *ortho*-palladation, regioselective C-H activation and flow under photochemical conditions. On the other hand, the main disadvantages of this methodology was the use of stoichiometric amounts of the expensive palladium salts and the multistep reaction sequence (Scheme 1b)[17].

The photoredox preparation of 1,2-diaminotruxinic derivatives through the head-to-head coupling of Erlenmeyer azlactones has not been previously described. Besides, the previous

reports of similar transformations could not access the desired compounds in high regio- and stereocontrol. In this context, we herein present two different methods for the preparation of 1,2-diaminotruxinic derivatives through photoredox catalysis. By changing the photocatalyst both symmetric or non-symmetric cyclobutane derivatives could be accessed as only one diastereomer (Scheme 1c).

Scheme 1. Previous reports on [2+2] photocycloaddition and this work proposal.



Results and discussion

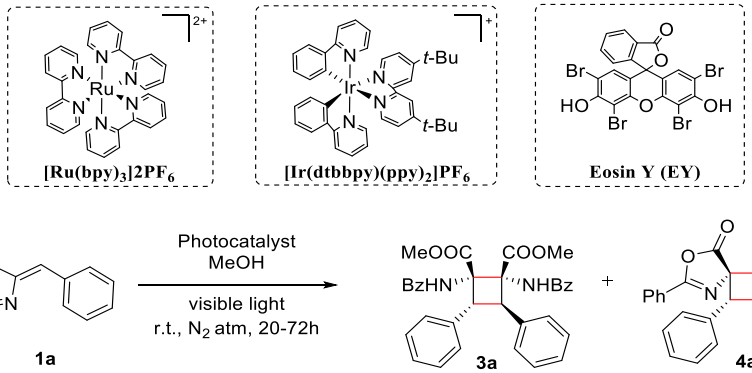
Initially, *Z*-Erlenmeyer azlactones were prepared following literature protocols.[10] Since most recent contributions in visible light photoredox reactions focused on activation of organic functional groups by transition metal catalysts such as $[Ru(bpy)_3]^{2+}$,[5,18] we decide to start our study investigating the reaction between azlactone **1a,** in the presence of 2 mol% of $Ru(bpy)_3(PF_6)_2$ and dichloromethane as solvent. To our delight, the desired product (**2a**) was obtained in 38% yield. However, the highly strained tricyclic system was unstable and cycloreversion was observed (Scheme 2). Thus, we envisioned that by switching the solvent to methanol, the azlactone ring opening of **2a** by the alcohol would reduce the strain in the tricyclic spiro type system and avoid the stability problems of the cycloadduct previously observed.

Scheme 2. [2+2] cycloaddition of an Erlenmeyer Azlactone in dichloromethane.

Then, the reaction optimization was carried out and the results are summarized in Table 1. In the presence of 2 mol% of $Ru(bpy)_3^{2+}$, azlactone **1a** was irradiated with 60W blue LED, affording the desired product **3a** in 37% yield and compound **4a** as a side product in 8% isolated yield (Entry 1). Two other visible-light catalysts were subsequently evaluated and showed to be inferior to $Ru(bpy)_3Cl_2$ (Entries 2 and 3). The use of the Lewis acid $LiBF_4$ additive and (±)-camphorsulfonic acid (CSA) increased the yield of **3a** to 52% (Entry 4). The use of $BF_3.Et_2O$ gave almost azlactone ring-opening product. Interestingly, the selectivity of the reaction changed by the use of Eosin Y (EY) as photocatalyst, affording the non-symmetric cycloadduct **4a** as major product (52% yield) (Entry 3). An increase of the catalyst loading, the use of green LEDs (30W) or DIPEA and $LiBF_4$ as additives did not increase the yield of **4a** (Entries 7-10). It is worth to mention that all reaction achieved conversions up to 99%.

We also observed that even in the presence of the photocatalyst, no cycloaddition took place in the absence of the light source and only ring opening azlactone starting materials were observed (Entries 11 and 12). Likewise, no cycloadducts were formed only by LED light irradiation, without photocatalyst (Entry 13). Furthermore, the addition of the photocatalyst to the azlactone ring opening products did not lead to cycloadducts, suggesting that these derivatives are not active for the formation of [2+2] cycloaddition products.

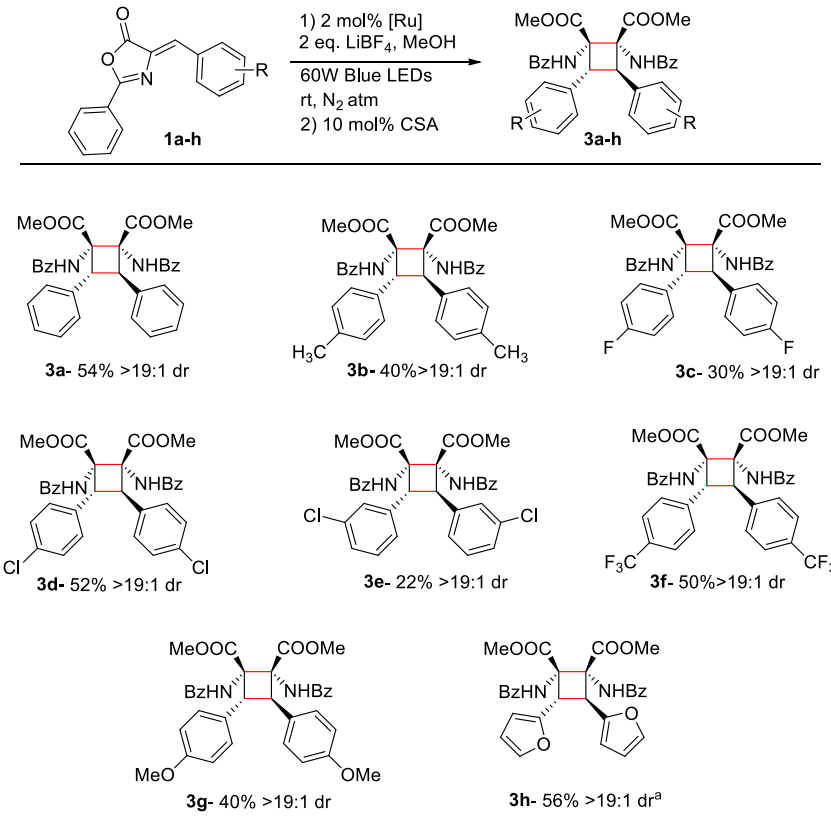
Table 1. Optimization and control studies for photocatalytic [2+2] cycloadditions.



Entry	Catalyst (mol%)	Light source (LEDs)	$LiBF_4$ (mol%)	Additive	Yield **3a** (%)[a]	Yield **4a** (%)[a]
1	Ru (2)	Blue	-	-	37%	8%
2	Ir (2)	Blue	-	-	23%	ND
3	EY (5)	Blue	-	-	Traces	52%
4	Ru (2)	Blue	2	CSA	52%	Traces
5	Ru (2)	Blue	2	DABCO	32%	ND
6	Ru (2)	Blue	2	NEt_3	35%[b]	ND
7	EY (10)	Blue	-	-	ND	29%
8	EY (5)	Green	-	-	ND	19%
9	EY (5)	Blue	-	DIPEA	0	0
10	EY (5)	Blue	3	-	ND	35%
11	EY (5)	-	-	-	0	0
12	Ru (2)	-	-	-	0	0
13	-	Blue	-	-	0	0

[a] Isolated yield after purification through flash chromatography; [b] conversion detected by ^1H NMR; ND: not determined (minor byproduct).

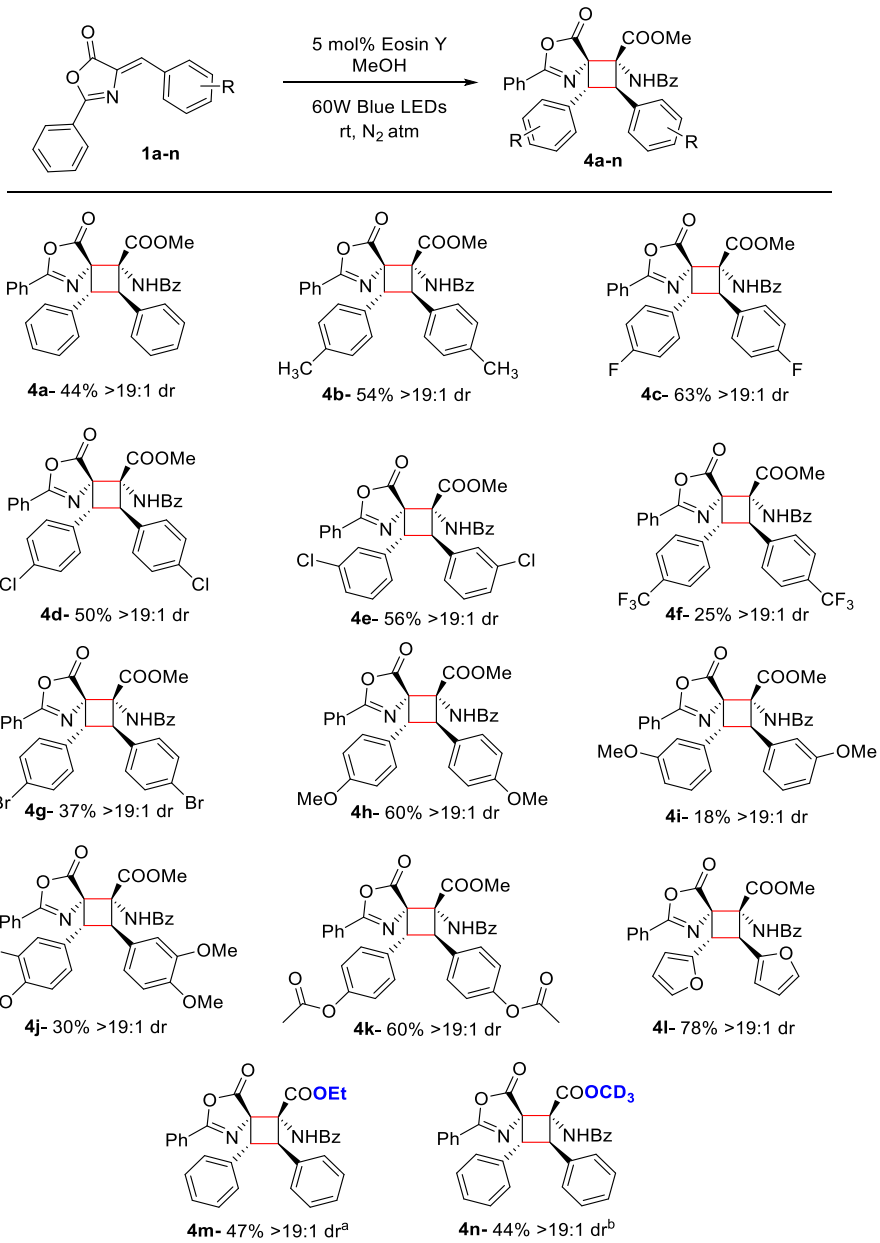
Having established a catalytic system for the stereoselective formation of symmetric and non-symmetric cyclobutanes, we proceeded to test the generality of this system. Initially, we examined the scope concerning the preparation of symmetrical cycloadducts **3a-h** (Scheme 3). In general, different substituted azlactones (**1a-h**) were well tolerated, with both electron-donating and electron-withdrawing substituents, affording the desired products in yields between 22-56% and with >19:1 dr. It is worth to mention, even the use of a *meta*-substituted azlactone was possible, although a modest yield was attained (22% yield). Moreover, the use of a heteroaryl oxazolone was also tolerated, affording product **3h** in 56% yield. We also examined the reaction in the presence of two different azlactones, unfortunately a complex mixture was observed.



Scheme 3. Preparation of symmetric 1,2-diaminotruxinic derivatives through a [2+2]-cycloaddition reaction using $Ru(bpy)_3Cl_2$ as catalyst.

[a] The reaction was carried out in the absence of CSA.

We next evaluated the scope concerning the formation of non-symmetric cyclobutane derivatives **4a-n** (Scheme 4). The reaction tolerated the use of heteroaryl and aryl azlactones bearing electron-donating and withdrawing substituents, affording a diverse scope of bicyclic spiro-type cyclobutanes with perfect diastereocontrol. By changing the reaction solvent to ethanol, the desired cyclobutane derivative **4m** was isolated in 47% yield. Isopropanol was also tested, but did not lead to the desired cycloaddition product.



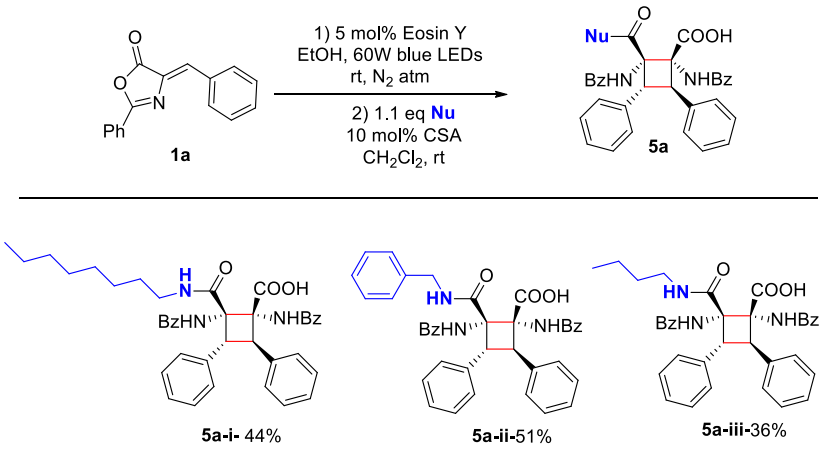
Scheme 4. Preparation of non-symmetric 1,2-diaminotruxinic derivatives through a [2+2]-cycloaddition reaction using Eosin Y as catalyst.

[a] Ethanol was used as solvent.

[b] Deuterated methanol was used as solvent.

In all cases, the NMR analysis of the crude reaction mixture revealed the presence of only one diastereomer. Thus, X-ray crystallographic analysis was carried out to elucidate the relative and absolute stereochemistry of compound **4d** (see Supporting Information). In this context, the single diastereomer 1,2-*Z*,*E*-*anti* (Zeta) was classified as an 1,2-amino truxinic derivative, since they are originated by the head-to-head *anti*-[2+2] cycloaddition of *Z*- and *E*-oxazolones.[17, 19, 20]

One important advantage of this catalytic system is the preservation of the versatile azlactone scaffold, allowing its potential application in a diversity of transformations [21]. Thus, we envisioned that the Brønsted acid catalyzed azlactone ring opening method previously reported by our group might be used to further functionalize the oxazolone moiety in cyclobutanes **4a-n**.[13] After a series of trials, we found a one-pot method for visible light induced [2+2] cycloaddition and azlactone ring opening (Scheme 5). Different amines could also be used in this reaction conditions, affording the desired compounds in good yields.



Scheme 5. O*ne-pot* visible light induced [2+2]-cycloaddition of Erlenmeyer azlactones/Brønsted acid catalyzed azlactone ring opening reaction sequence.

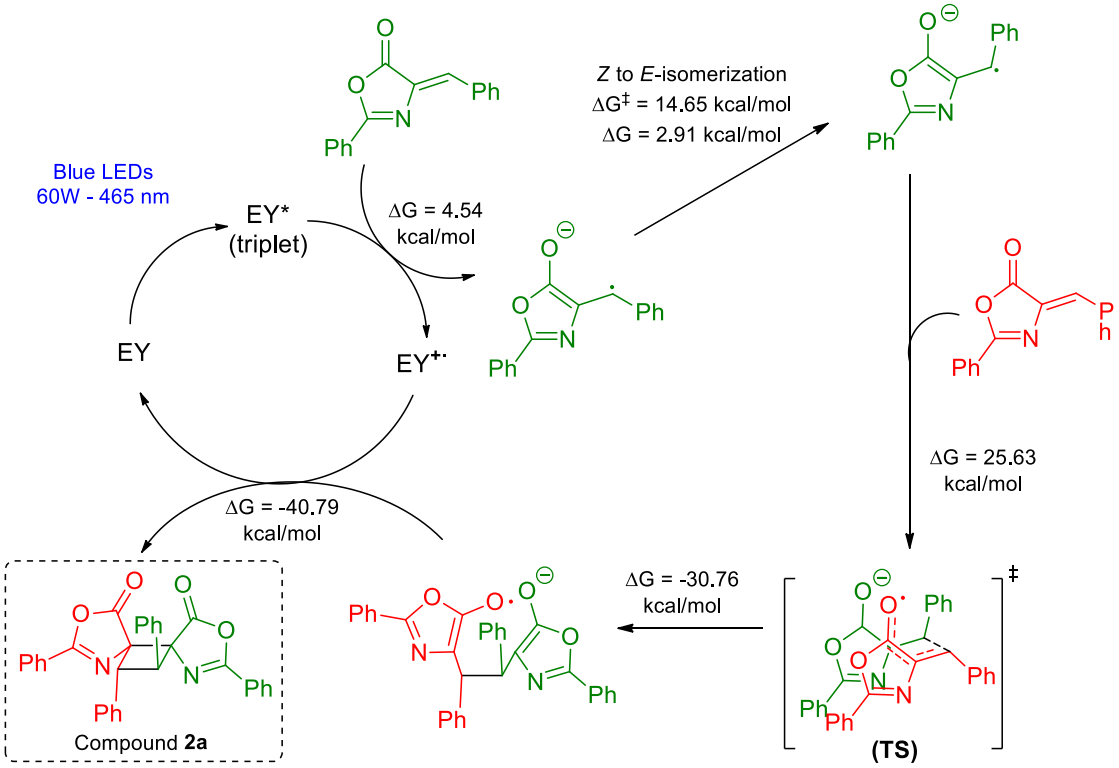
We next turned our attention towards the comprehension of the reaction mechanism (Scheme 6). Initially, based on our group previous studies involving the mechanism of azlactone ring-opening reaction (RO) in the presence of CSA[13,22] and based on control experiments during the optimization (that revealed that the ring-opened azlactone derivative is inactive in photoredox conditions), we believe that the RO step occurs after the cycloaddition reaction, affording either **3a-3h** (two RO reactions) or **4a-4n** (one RO reaction - in the presence of the eosin Y acting as a Brønsted acid). Due to that, since we believe that product **2a** is a common intermediate in both pathways, we decided to evaluate its formation. To this purpose, theoretical calculations were performed (all data concerning the calculations is available in the SI). It is important to mention, the reaction failed in the absence of light.

Initially, TD-DFT calculation of the first singlet and triplet states of the eosin Y catalyst were performed and revealed that only the triplet state is compatible with the blue light LED energy (the triplet data showed perfect accordance with experimental data - reported: 1.89 *e*V; calculated: 1.89 *e*V). This excited state then can follow by two possible pathways: the electron transfer between catalyst and azlactone, affording the eosin Y radical anion or cation. The

$EY^{+\bullet}$/azlactone$^{-\bullet}$ formation showed to be favored over $EY^{-\bullet}$/azlactone$^{+\bullet}$ and unselective for oxazolone isomers (ΔG 4.2-4.5 against 17.9-18.9 kcal/mol).

For the formation of **2a**, a reaction between the *E* and *Z* Erlenmeyer azlactones is required for the formation of the desired diastereomer. Since initially only the *Z* isomer was employed, the photo-mediated isomerization must take place.[16,17] The isomerization barrier of neutral oxazolone is incompatible with a reaction that proceeds at room temperature, however, when *Z*-azlactone radical anion is formed by the electron transfer with the excited (triplet) eosin Y catalyst, the isomerization can occur, affording *E*-azlactone radical anion with a calculated $\Delta G^{\ddagger}$ of 14.65 kcal/mol and a reaction ΔG of only 2.91 kcal/mol.

Having established an initial mechanism, we next investigated the cycloaddition steps. In an attempt to explain the stereoselectivity, the formation of all possible head-to-head diastereomers were evaluated (1,2-*Z*,*E*-*anti*; 1,2-*E*,*E*-*anti*; 1,2-*Z*,*Z*-*anti*; 1,2-*Z*,*E*-*syn*; 1,2-*E*,*E*-*syn* and 1,2-*Z*,*Z*-*syn*). By our proposal, initially, the azlactone radical anion (either *Z* or *E*) reacts with a neutral Erlenmeyer azlactone ($\Delta G^{\ddagger}$ = 21.6-27.4 kcal/mol), affording a radical anion dimer in which the 4-membered ring moiety has not been formed yet. It is worth mentioning that this intermediate is thermodynamically favored only for the coupling of *E*-*E* and *Z*-*E* azlactones (ΔG = -2.9 to -7.8 kcal/mol) and that, since the *E* azlactone occurs only in small amounts during the reaction, the *E*-*E* coupling is less likely to occur. Furthermore, the *anti* coupling is favored when compared to *syn* addition (*anti* = -5.12 to -7.8 kcal/mol; *syn* = -2.9 to -3.6 kcal/mol); we propose that this is the step in which the configuration of the product is determined and that the sum of these observations makes the formation of 1,2-*Z*,*E*-*anti* the most probable to occur. Finally, this step is then followed by an electron transfer of this intermediate to the $EY^{+\bullet}$, with immediate ring-closure of the cyclobutane moiety, and formation of product **2a**, thus regenerating the neutral eosin catalyst. This step is greatly thermodynamically favored, with a ΔG between -34.5 and -45.9 kcal/mol. The full mechanistic proposal for the isolated product is summarized in Scheme 6 and the Gibbs Free Energies for the formation of all diastereomers is available in the SI.



Scheme 6. Proposed catalytic cycle.

Conclusions

In summary, two highly regio- and diastereoselective conditions to obtain cyclobutane precursors of 1,2-diaminotruxillic acid derivates have been presented. The reaction takes place in methanol, in the presence of photocatalyst under visible light photoredox catalysis approach. From the reaction condition B, in which the azlactone ring moiety is incorporated in the product, a *one-pot* method to further functionalize these derivatives was developed employing a subsequent ring opening reaction. DFT studies were carried out and showed an interaction between the azlactone radical anion and neutral *E*-azlactone leading to the product. To the best of our knowledge, this consists the first report of stereoselective head-to-head coupling of Erlenmeyer-Plöchl azlactones.

Experimental Section

General Information. All purchased chemicals were used as received without further purification. Solvents were dried according to standard procedures. Analytical thin layer chromatography (TLC) was performed on TLC plates (silica gel 60 F254) and visualized by a UV

lamp. Column flash chromatography was performed using 230-400 mesh silica gel. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 7.26 ppm. Chemical shifts for $^{13}C\{^{1}H\}$ NMR were reported as δ, parts per million, relative to the center line signal of the $CDCl_3$ triplet at 77 ppm. The ^{1}H NMR spectra were recorded at 500 MHz, ^{13}C NMR spectra were recorded at 125 MHz. Chemical shifts are reported in ppm using the following peak pattern abbreviations: br, broad; s, singlet; d, doublet; dd, double doublet; ddd, doublet of doublet of doublets; t, triplet; dt, double triplet; q, quartet; pent, pentet; sext, sextet; m, multiplet. High-resolution mass spectra were acquired in the Matrix–assisted laser desorption/ionization time of flight (MALDI-TOF) spectrometer using a pulsed nitrogen laser at 337 nm. Single-crystal data for compound **4d** were collected using an Oxford Diffraction Gemini A Ultra diffractometer with CuKα (λ=1.54184 Å) at 150 K. Data collection, reduction and cell refinement were performed using the CrysAlis PRO 1.171.39.46e program (Rigaku OD, 2018) Oxford Diffraction Ltd. The structure was solved and refined using the ShelXT[24], SHELXL[25] and Olex2[26]. A Multi-scan absorption correction CrysAlis PRO 1.171.39.46e (Rigaku Oxford Diffraction, 2018) was used. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. Anisotropic displacement parameters were assigned to all non-hydrogen atoms bound to oxygen and nitrogen. The H atoms were initially located in a difference Fourier map, added in idealized positions and further refined according to the riding model: N-H = 0.86 Å, and Uiso (H) = 1. 2 Ueq (N). The C-bound H atoms were included in the riding-model approximation: C-H = 0.95 Å and Uiso (H) = 1.2Ueq(C). The structure representation was plotted using ORTEP for Windows[27].

Additional details of the data collections and structural refinement parameters are provided in the SI. Selected bond lengths, angles and are listed in Table S5 of the SI. CCDC 866124 are the supplementary crystallographic data for this paper. It can be obtained freely from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. Melting points were recorded respectively on a melting point apparatus.

General procedures for the Synthesis of compounds 1a-l

A mixture of hippuric acid (5.0 mmol), anhydrous NaOAc (5.0 mmol), acetic anhydride (5.0 mL) and the appropriate aldehyde (5.0 mmol) was heated in oil bath to 95°C for 4h. After completion of reaction (monitored by TLC), the contents were cooled and washed with a solution of water/ethanol 2:1. The crude was filtered off and the crystals were obtained by recrystallization with ethanol.

(Z)-4-benzylidene-2-phenyloxazol-5(4H)-one (1a).[28] The product was obtained as a light yellow crystal (880 mg, 70 %). Mp: 156.2-156.5°C. FT-IR (ZnSe, cm^{-1}) ν 1788, 1764, 1649, 1156, 678. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.22-8.19 (m, 4H), 7.62 (tt, 1H, *J* = 7.4, 1.25 Hz), 7.54 (t, 2H, *J* = 7.90 Hz), 7.51-7.46 (m, 3H), 7.27 (s, 1H). ^{13}C {^{1}H} NMR (125MHz) δ: 167.8, 163.7, 133.7, 133.5, 133.4, 132.6, 132.0, 131.4, 129.1, 129.1, 128.5.

(Z)-4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-one (1b).[28] The product was obtained as a yellow crystal (796.0 mg, 60 %). Mp: 134.8-134.9°C. FT-IR (ZnSe, cm^{-1}) ν 1789, 1766, 1647, 1156, 980, 816, 691.^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (d, 2H, *J* = 7.10 Hz), 8.11 (d, 2H, *J* = 8.3 Hz), 7.62 (tt, 1H, *J* = 7.30 Hz, *J* = 1.30 Hz), 7.53 (t, 2H, *J* = 7.70 Hz), 7.29 (d, 2H, *J* = 8.00 Hz), 7.24 (s, 1H), 2.43 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz) δ: 168.0, 163.2, 142.3, 133.3, 132.7, 132.6, 132.2, 131.1, 129.9, 129.1, 128.5, 128.4, 125.9, 22.0.

*(Z)-4-(4-fluorobenzylidene)-2-phenyloxazol-5(4H)-one (1c)***.**[29] The product was obtained as a light yellow crystal (935.0 mg, 70%). Mp: 176.9-178.8°C. FT-IR (ZnSe, cm^{-1}) ν 1792, 1653, 1594, 1499, 1155, 981, 865, 829, 694, 684. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (dd, 2H, *J* = 8.75, 5.6 Hz), 8.18 (dd, 2H, *J* = 8.2, 1.4 Hz), 7.62 (tt, 1H, *J* = 7.45, 1.25 Hz), 7.53 (t, 2H, *J* = 7.85 Hz), 7.20 (s, 1H), 7.17 (t, 2 H, *J* = 8.65 Hz). ^{13}C {^{1}H} NMR (125 MHz) δ: 167.7, 164.4 (d, *J* = 253.2 Hz), 163.8, 134.9, 134.8 (d, *J* = 8.6 Hz), 133.6, 133.1, 133.0, 130.5, 130.1, 130.0, 129.1, 128.5, 125.7, 116.2 (d, *J* = 21.8 Hz).

(Z)-4-(4-chlorobenzylidene)-2-phenyloxazol-5(4H)-one (1d).[29] The product was obtained as a light yellow crystal (895.0 mg, 63%). Mp: 187.5-187.8°C. FT-IR (ZnSe, cm^{-1}) ν 1790, 1654, 1164, 867, 827, 692.^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (d, 2H, *J*= 7.20 Hz), 8.15 (d, 2H, *J*= 8.50 Hz), 7.63 (t, 1H, *J* = 7.40 Hz), 7.54 (t, 2H, *J* = 7.40 Hz), 7.45 (d, 2H, *J* = 8.65 Hz), 7.18 (s, 1H). ^{13}C {^{1}H} NMR (125 MHz) δ: 167.5, 164.1, 137.4, 133.7, 132.2, 130.2, 129.4, 129.2, 128.6, 125.6.

*(Z)-4-(3-chlorobenzylidene)-2-phenyloxazol-5(4H)-one (1e)***.** The product was obtained as a light yellow crystal (938.0 mg, 67%). Mp: 174.0-175.0°C. FT-IR (ZnSe, cm^{-1}) ν 1790, 1654, 1164, 867, 819, 692. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.30-8.29 (m, 1H), 8.20-8.18 (m, 2H), 8.01-7.99 (m, 1H), 7.64 (tt, 1H, *J* = 7.45, 1.30 Hz), 7.57-7.53 (m, 2H), 7.43-7.39 (m, 2H). ^{13}C {^{1}H} NMR (125 MHz) δ: 167.5, 164.1, 137.4, 133.7, 132.2, 130.2, 129.4, 129.2, 128.6, 125.6.

(Z)-4-(4-bromobenzylidene)-2-phenyloxazol-5(4H)-one (1f).[29] The product was obtained as a light yellow crystal (1.06 g, 65%). Mp: 196.8-197.0°C. FT-IR (ZnSe, cm^{-1}) ν 1785, 1761, 1653, 818, 693. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.18 (dd, 2H, *J* = 8.3, 1.4 Hz), 8.07 (d, 2H, *J* = 8.45 Hz), 7.65-7.59 (m, 3H), 7.54 (t, 2H, *J* = 7.85 Hz), 7.16 (s, 1H). ^{13}C {^{1}H} NMR (125 MHz) δ: 167.5, 164.1, 133.9, 133.8, 133.7, 132.5, 132.4, 130.2, 129.2, 128.6, 126.1, 125.6.

(Z)-2-phenyl-4-(4-(trifluoromethyl)benzylidene)oxazol-5(4H)-one (1g).[30] The product was obtained as a light yellow crystal (885.0 mg, 56%). Mp: 174.0-175.0°C. FT-IR (ZnSe, cm^{-1}) ν 1793, 1652, 1554, 1315, 837, 687. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.30 (d, 2H, *J*= 8.20 Hz), 8.19-8.17 (m, 2H), 7.72 (d, 2H, *J*= 8.25 Hz), 7.64 (tt, 1H, *J*= 7.45, 1.9 Hz), 7.56-7.53 (m, 2H), 7.22 (s, 1H). ^{13}C {^{1}H} NMR (125 MHz) δ: 167.2, 164.9, 136.8, 135.3, 134.0, 132.0 (q, *J* = 32.4 Hz), 129.2, 129.2, 128.8, 125.7 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 270.6 Hz).

(Z)-4-(4-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (1h).[28] The product was obtained as a light yellow crystal (945.0 mg, 68%). Mp: 162.0-163.2°C. FT-IR (ZnSe, cm^{-1}) ν 1788, 1771, 1599, 1260, 1163, 830, 704. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.21-8.16 (m, 4H), 7.59 (tt, 1H, *J* = 7.35, 1.25 Hz), 7.54-7.51 (m, 2H), 7.22 (s, 1H), 7.00 (d, 2H, *J* = 9 Hz). ^{13}C {^{1}H} NMR (125 MHz) δ: 168.2, 162.4, 134.7, 133.1, 132.1, 131.3, 129.1, 128.3, 126.7, 126.0, 114.7, 55.6.

(Z)-4-(3-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (1i). The product was obtained as a light yellow crystal (834.0 mg, 60%). Mp: 103.5-104°C. FT-IR (ZnSe, cm^{-1}) ν 1802, 1652, 1581, 1280, 766. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17-8.15 (m, 2H), 7.93-7.94 (m, 1H), 7.66 (d, 1H, *J* = 7.65 Hz), 7.61 (tt, 1H, *J* = 7.40, 1.25 Hz), 7.54-7.51 (m, 2H), 7.38 (t, 1H, *J* = 8.00 Hz), 7.21 (s, 1H), 7.02 (ddd, 1H, *J* = 8.25, 2.65, 0.85 Hz), 3.91 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz) δ: 167.7, 163.7, 159.9, 134.8, 133.5, 131.8, 129.9, 129.1, 128.5, 125.7, 125.6, 117.9, 116.7, 55.5.

(Z)-4-(3,4-dimethoxybenzylidene)-2-phenyloxazol-5(4H)-one (1j). The product was obtained as a light yellow crystal (986.0 mg, 64%). Mp: 154.2-155.0°C. FT-IR (ZnSe, cm^{-1}) ν 1782, 1762, 1647, 1591, 1240, 692. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15-8.10 (m, 3H), 7.58-7.49 (m, 4H), 7.18 (s, 1H), 6.92 (d, 1H, *J* = 8.35 Hz), 4.01 (s, 3H), 3.95 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz) δ: 168.0, 162.5, 152.2, 149.3, 133.1, 132.2, 131.3, 129.1, 128.1, 127.9, 127.0, 125.9, 114.1, 111.0, 56.1, 56.0.

(Z)-4-((5-oxo-2-phenyloxazol-4(5H)-ylidene)methyl)phenyl acetate (1k).[30] The product was obtained as a light yellow crystal (989.0 mg, 65%). Mp: 171.8-172.3°C. FT-IR (ZnSe, cm^{-1}) ν 1796, 1759, 1651, 1219, 1160, 857, 696. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.24 (d, 2H, J = 8.50 Hz), 8.18 (d, 2H, J = 7.30 Hz), 7.62 (t, 1H, J = 7.50 Hz), 7.54 (t, 2H, J = 7.70 Hz), 7.23-7.22 (m, 3H), 2.34 (s, 3H). ^{13}C {^1H} NMR (125 MHz) δ: 169.1, 167.7, 163.8, 152.8, 133.9, 133.6, 133.4, 131.4, 130.7, 129.1, 128.5, 125.7, 122.3, 21.3.

(Z)-4-(furan-2-ylmethylene)-2-phenyloxazol-5(4H)-one (1l).[29] The product was obtained as a brown crystal (657.0 mg, 55%). Mp: 191.2-191.3°C. FT-IR (ZnSe, cm^{-1}) ν 1789, 1654, 1156, 699. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.14 (dd, 2H, *J* = 8.3, 1.2 Hz), 8.11 (m, 1H), 7.60 (tt, 1H, *J* = 7.4, 1.3 Hz), 7.54-7.51 (m, 3H), 7.26-7.25 (m, 1H), 7.20 (s, 1H). ^{13}C {^1H} NMR (125 MHz) δ: 167.2, 162.6, 148.0, 144.5, 133.3, 132.9, 129.1, 128.3, 125.8, 121.5, 111.,3.

General procedures for the Synthesis of compounds 2a

The product was prepared using an oven-dried 4 mL vial equipped with a Teflon septum and magnetic stir bar. It was charged with tris-(2,2´-bipyridyl)ruthenium (II) chloride hexafluorophosphate (0.02 equiv), the Erlenmeyer-Plöchl azlactone **1a** (0,039g, 0.15 mmol), and CH_2Cl_2 (2.0 mL, C = 0.075M). The vial was purged with nitrogen, sealed with parafilm and placed approximately 8 cm from a 60 W blue LEDs. After the reaction was complete (as judged by TLC analysis) and concentrated *in vacuo*. 24 h reaction time. The product was purified by flash chromatography in 5% of ethyl acetate in hexane.

(5R,6R)-11,12-bis(4-chlorophenyl)-2-phenyl-3,9-dioxa-1,7-diazadispiro[4.0.46.25]dodeca-1,7-diene-4,10-dione (2a). The product was obtained as a white solid (13.8 mg, 35%). Mp: 141.2-142°C. FT-IR (ZnSe, cm^{-1}) ν 1816, 1629, 987, 878, 696. ^1H NMR (500MHz, $CDCl_3$): δ 8.02 (dd, 4H, *J* = 8.3, 1.1 Hz), 7.59 (tt, 2H, *J* = 7.45, 1.25 Hz), 7.46 (t, 4H, *J* = 8.15 Hz), 7.29 (d, 4H, *J* = 8.5 Hz), 5.15 (s, 2H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 172.4, 164.3, 134.3, 133.9, 133.5, 129.4, 129.0, 128.8, 128.5, 124.8, 77.0, 45.9.HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{21}Cl_2N_2O_4^+$ 567.0873, found 567.0870.

General procedures for the Synthesis of compounds 3a-h

Condition A: [2+2]-photocycloaddition of Erlenmeyer–Plöchl Azlactone using $Ru(bpy)_3Cl_2$ as catalyst. An oven-dried 4 mL vial equipped with a Teflon septum and magnetic stir bar was charged with tris-(2,2´-bipyridyl)ruthenium (II) chloride hexahydrate (3.0 µmol, 0.02 equiv), the corresponding Erlenmeyer-Plöchl's azlactone (0.15 mmol, 1.0 equiv), and $LiBF_4$ (0.3 mmol, 2

equiv) and MeOH (2.0 mL, C = 0.075M). The vial was sealed with parafilm and placed approximately 8 cm from a 60 W blue LEDs. After the reaction was complete (as judged by TLC analysis) CSA was added. After 24 hours stirring at room temperature, the reaction was concentrated in vacuo, liquid-liquid extraction in dichloromethane/$NaHCO_3$ (saturated solution) (2x) and dichloromethane/H_2O (1x). The organic phase was dried with anhydrous sodium sulfate, filtrated and the solvent was concentrated in vacuo.

Dimethyl-1,2-bis(benzamido)-3,4-diphenylcyclobutane-1,2-dicarboxylate (3a). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (22.8 mg, 54%). 5 days reaction time. Mp: 79.6-80.6°C. FT-IR (ZnSe, cm^{-1}): 3059, 2922, 1731, 1640, 1515, 1476, 1214, 685. ^{1}H NMR (500MHz, $CDCl_3$): δ (ppm): 8.27 (br, 2H), 7.54 (d, 4H, *J* = 7.35 Hz), 7.45-7.46 (m, 6H), 7.36 (t, 4H, *J* = 7.75 Hz), 7.31 (t, 4H, *J* = 7.6 Hz), 7.25-7.26 (m, 2H), 4.91 (s, 2H), 3.73 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm): 171.7, 166.7, 134.8, 133.4, 131.9, 129.2, 128.8, 128.7, 128.3, 127.0, 64.2, 53.1, 47.6. HRMS (MALDI) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{31}N_2O_6^+$ 563.2177, found 563.2192.

Dimethyl 1,2-bis(benzamido)-3,4-di-p-tolylcyclobutane-1,2-dicarboxylate (3b). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (17.7 mg, 40%). 2 days reaction time. Mp: 79.0-80.2°C. FT-IR (ZnSe, cm^{-1}): 2917, 1730, 1668, 1473, 1297, 712. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.30 (br, 2H), 7.58 (d, 4H, *J* = 7.30 Hz), 7.47 (t, 4H, *J* = 7.30 Hz), 7.37 (t, 4H, *J* = 7.70 Hz), 7.33 (d, 4H, *J* = 7.9 Hz), 7.11 (d, 4H, *J* = 7.80 Hz), 4.84 (s, 2H), 3.71 (s, 6H), 2.28 (s, 2H). ^{13}C {^{1}H} (125MHz, $CDCl_3$) δ (ppm): 171.8, 166.9, 138.0, 131.9, 131.8, 129.6, 129.1, 128.7, 127.1, 64.3, 53.1, 47.6, 21.3. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ calcd for $C_{36}H_{34}KN_2O_6^+$ 629.2048, found 629.2028.

Dimethyl 1,2-bis(benzamido)-3,4-bis(4-fluorophenyl)cyclobutane-1,2-dicarboxylate (3c). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (13.5 mg, 30%). 2 days reaction time. Mp 205-205.1°C. FT-IR (ZnSe, cm^{-1}): 3351, 2952, 1721, 1668, 1509, 1208, 703. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.15 (s, 2H), 7.56 (m, 4H), 7.49 (m, 2H), 7.40 (m, 8H), 7.00 (m, 4H), 4.83 (s, 2H), 3.73 (s, 6H). ^{13}C {^{1}H} (125MHz, $CDCl_3$) δ (ppm): 171.6, 166.9, 162.8 (d, $J_{C\text{-}F}$ = 246.0 Hz), 133.2, 132.2, 130.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 130.4 (d, $J_{C\text{-}F}$ = 3.1 Hz), 128.9, 127.1, 115.9 (d, $J_{C\text{-}F}$ = 21.3 Hz), 64.3, 53.3, 47.2. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{28}F_2N_2NaO_6^+$ 621.1808, found 621.1835.

Dimethyl 1,2-bis(benzamido)-3,4-bis(4-chlorophenyl)cyclobutane-1,2-dicarboxylate (3d). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (24.6 mg, 52%). 5 days reaction time. Mp: 84.7-85.7°C. FT-IR (ZnSe, cm^{-1}): 2917, 1721, 1667, 1473, 1083, 1013, 712. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.14 (br, 2H), 7.58-7.56 (m, 4H), 7.51-7.48 (m, 2H), 7.42-7.38 (m, 4H), 7.37-7.35 (m, 4H), 7.29-7.27 (m, 4H), 4.82 (s, 2H), 3.73 (s, 6H). ^{13}C {^1H} (125MHz, $CDCl_3$) δ (ppm): 171.4, 166.9, 134.5, 133.1, 133.0, 132.3, 130.4, 129.1, 128.9, 127.1, 64.4, 53.4, 47.1. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{28}N_2O_6Cl_2Na^+$ 653.1217, found 653.1246.

Dimethyl 1,2-bis(benzamido)-3,4-bis(3-chlorophenyl)cyclobutane-1,2-dicarboxylate (3e). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (10.4 mg, 22%). 24h reaction time. Mp: 132.9-133.4°C. FT-IR (ZnSe, cm^{-1}): 2917, 1730, 1456, 1031, 676. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.31 (s, 2H), 7.58 (d, 4H, *J* = 7.15 Hz), 7.47 (t, 2H, *J* = 7.45 Hz), 7.38 (t, 4H, *J* = 7.70 Hz), 7.23 (t, 2H, *J* = 7.95 Hz), 7.06 (d, 2H, *J* = 7.45 Hz), 6.96 (s, 2H), 6.79 (d, 2H, *J* = 8.30 Hz), 4.83 (s, 2H), 3.72 (s, 6H). ^{13}C {^1H} (125MHz, $CDCl_3$) δ (ppm): 171.7, 166.9, 159.9, 136.5, 133.5, 132.0, 129.9, 128.8, 127.2, 121.5, 115.0, 113.9, 64.3, 53.2, 47.9. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{34}H_{28}N_2O_6Cl_2Na^+$ 653.1217, found 653.1240.

Dimethyl 1,2-bis(benzamido)-3,4-bis(4-(trifluoromethyl)phenyl)cyclobutane-1,2-dicarboxylate (3f). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (26.2 mg, 50%). 5 days reaction time. Mp: 73.7-74.3°C. FT-IR (ZnSe, cm^{-1}): 3333, 2952, 1721, 1668, 1482, 1323, 703. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.07 (s, 2H), 7.56 (s, 8H), 7.53-7.48 (m, 6H), 7.39 (t, 4H, *J* = 7.75 Hz), 4.98 (s, 2H), 3.76 (s, 6H). ^{13}C {^1H} (125MHz, $CDCl_3$) δ (ppm): 171.2, 167.1, 138.6, 132.9, 132.4, 130.7 (q, J_{C-F} = 32.3 Hz), 129.5, 128.9, 127.0, 125.8 (q, J_{C-F} = 3.6 Hz), 124.1 (q, J_{C-F} = 270.7 Hz), 64.7, 53.5, 47.1. HRMS (MALDI) *m/z*: $[M+K]^+$ calcd for $C_{36}H_{28}F_6KN_2O_6^+$737.1483, found 737.1477.

Dimethyl 1,2-bis(benzamido)-3,4-bis(4-methoxyphenyl)cyclobutane-1,2-dicarboxylate (3g). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as a white solid (18.7 mg, 40%). 5 days reaction time. Mp: 79.0-80.8°C. FT-IR (ZnSe, cm^{-1}): 2917, 1721, 1659, 1518, 1464, 1252, 703. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.27 (br, 2H), 7.57 (d, 4H, *J* = 8.05 Hz), 7.47 (t, 2H, *J* = 7.45 Hz), 7.37 (t, 8H, *J* = 7.55 Hz), 6.85 (d,

4H, *J* = 8.45 Hz), 4.79 (s, 2H), 3.74 (s, 6H), 3.71 (s, 6H). $^{13}C\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 171.8, 166.8, 159.5, 133.4, 131.9, 130.3, 128.7, 127.1, 126.7, 114.2, 64.2, 55.4, 53.1, 47.4. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{36}H_{34}N_2NaO_8^+$645.2207, found 645.2237.

Dimethyl 1,2-bis(benzamido)-3,4-di(furan-2-yl)cyclobutane-1,2-dicarboxylate (3h). The product was prepared according to the Condition A and obtained after flash chromatography in 30% of ethyl acetate in hexane as an oil (45.5 mg, 56%). 5 days reaction time. FT-IR (ZnSe, cm^{-1}): 3342, 2917, 1730, 1659, 1464, 712. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.29 (s, 2H), 7.66-7.62 (m, 5H), 7.51-7.48 (m, 5H), 7.39-7.37 (m, 8H), 4.45 (s, 2H), 3.69 (s, 6H). $^{13}C\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 171.9, 166.9, 143.9, 141.9, 133.2, 132.2, 128.9, 128.7, 127.2, 126.3, 120.2, 111.0, 63.8, 53.3, 41.2. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{30}H_{26}N_2NaO_8^+$ 565.1581, found 565.1575.

General procedures for the Synthesis of compounds 4a-n

Conditions B: [2+2]-photocycloaddition of Erlenmeyer–Plöchl Azlactone using Eosin Y as catalyst. An oven-dried 4 mL vial equipped with a Teflon septum and magnetic stir bar was charged with Eosin Y (0.05 equiv), the corresponding Erlenmeyer-Plöchl azlactone (0.15 mmol, 1.0 equiv) and MeOH (2.0 mL, C = 0.075M). The vial was sealed with parafilm and placed approximately 8 cm from a 60 W blue LEDs. After the reaction was complete (as judged by TLC analysis) and concentrated in vacuo.

Methyl 1-benzamido-8-oxo-2,3,6-triphenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4a). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (17.5 mg, 44%). 3 days reaction time. Mp: 177.2-178.2°C. FT-IR (ZnSe, cm^{-1}): 2915, 1810, 1731, 1640, 1503, 1476, 696. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.08 (d, 2H, *J* = 7.55 Hz), 7.65- 7.63 (m, 3H), 7.58-7.53 (m, 5H), 7.49 (t, 1H, *J* = 7.25 Hz), 7.42- 7.39 (m, 2H), 7.31-7.18 (m, 9H), 5.19 (d, 1H, *J* = 12.35 Hz), 4.71 (d, 1H, *J* = 12.35 Hz), 3.82 (s, 3H). $^{13}C\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 173.3, 169.3, 167.0, 164.0, 135.4, 135.0, 133.9, 133.5, 132.0, 129.1, 129.0, 128.7, 128.7, 128.7, 128.4, 128.1, 127.9, 127.1, 127.0, 75.8, 66.3, 53.1, 48.1, 44.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{27}N_2O_5^+$ 531.1914, found 531.1928.

Methyl 1-benzamido-8-oxo-6-phenyl-2,3-di-p-tolyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4b). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (22.6 mg, 54%). 3 days reaction time. Mp: 176.8-177.2°C. FT-IR (ZnSe, cm^{-1}): 3381, 2909, 1819, 1738, 1666, 1509, 1280, 713, 702. ^1H

(500 MHz, $CDCl_3$) δ (ppm): 8.06 (d, 2H, *J* = 7.95 Hz), 7.66-7.22 (m, 3H), 7.54-7.47 (m, 4H), 7.44-7.40 (m, 4H), 7.10-7.06 (m, 6H), 5.10 (d, 1H, *J* = 12.6 Hz), 4.63 (d, 1H, *J* = 12.5 Hz), 3.81 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H). ^{13}C {^1H} (125MHz, $CDCl_3$) δ (ppm): 173.4, 169.4, 167.1, 163.8, 137.8, 137.5, 133.8, 133.8, 132.4, 131.9, 131.9, 129.7, 129.2, 129.1, 128.7, 128.7, 128.6, 127.2, 127.0, 75.9, 66.3, 53.1, 48.0, 44.1, 21.3, 21.2. HRMS (MALDI) *m/z*: $[M+Na]^+$calcd for $C_{35}H_{30}N_2NaO_5^+$ 581.2047, found 581.2028.

Methyl 1-benzamido-2,3-bis(4-fluorophenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4c). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (26.8 mg, 63%). 5 days reaction time. Mp: 60.2-61.2°C. FT-IR (ZnSe, cm^{-1}): 2921, 1744, 1640, 1503, 1214, 732, 709, 687. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.08 (d, 2H, *J* = 7.70 Hz), 7.68-7.64 (m, 3H), 7.58-7.50 (m, 6H), 7.44-7.41 (m, 2H), 7.18-7.15 (m, 2H), 6.99-6.95 (m, 4H), 5.12 (d, 1H, *J* = 12.5 Hz), 4.58 (d, 1H, *J* = 12.7 Hz), 3.81 (s, 3H). ^{13}C {^1H} (125MHz, $CDCl_3$) δ (ppm): 172.9, 169, 167.1, 164.3, 161.6 (d, *J* = 245.7 Hz), 161.5 (d, *J* = 245.1 Hz), 134.2, 133.2, 132.2, 130.8 (d, *J* = 14.9 Hz), 130.7 (d, *J* = 14.8 Hz), 130.3, 130.2, 129.2, 128.9, 128.8, 128.7, 127.1, 124.7, 116.2 (d, *J* = 21.5 Hz), 115.3 (d, *J* = 21.3 Hz), 75.6, 66.2, 53.2, 47.9, 43.8. HRMS (MALDI) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{25}F_2N_2O_5^+$567.1726, found 567.1732.

Methyl 1-benzamido-2,3-bis(4-chlorophenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4d). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (23 mg, 50%). 5 days reaction time. Mp: 70.8-71.8°C. FT-IR (ZnSe, cm^{-1}): 2922, 1810, 1627, 1463, 698. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.07 (dd, 2H, *J* = 8.35, 1.2 Hz), 7.69-7.64 (m, 3H), 7.59 (s, 1H), 7.55 (t, 2H, *J* = 7.75 Hz), 7.51 (dt, 1H, *J* = 7.4, 1.3 Hz), 7.47 (d, 2H, *J* = 8.35 Hz), 7.43 (t, 2H, *J* = 7.8 Hz), 7.23-7.21 (m, 4H), 7.11 (d, 2H, *J* = 8.25 Hz), 5.10 (d, 1H, *J* = 12.4 Hz), 4.57 (d, 1H, *J* = 12.5 Hz), 3.80 (s, 3H). ^{13}C {^1H} (125MHz, $CDCl_3$) δ (ppm): 172.8, 169.0, 167.1, 164.4, 134.4, 134.2, 133.9, 133.5, 133.4, 133.2, 132.2, 130.0, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 127.2, 124.7, 75.5, 66.3, 53.3, 47.9, 43.8. HRMS (MALDI) *m/z*: $[M+K]^+$ calcd for $C_{33}H_{24}Cl_2KN_2O_5^+$ 637.0694, found 637.0706.

Methyl 1-benzamido-2,3-bis(3-chlorophenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4e). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (23 mg, 50%). 5 days reaction time. Mp: 151.5-152.2 °C. FT-IR (ZnSe, cm^{-1}): 2952, 1819, 1730, 1633, 1482, 1297, 685. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.07 (d, 2H, *J* = 7.35Hz), 7.69-7.65 (m, 3H), 7.59 (s, 1H), 7.56 (t, 2H, *J* = 7.80 Hz), 7.51 (d, 2H, *J* = 7.40 Hz), 7.47-7.42 (m, 3H), 7.23-7.21 (m, 4H), 7.08 (d, 1H, *J* = 6.65 Hz), 5.11 (d, 1H, *J* = 12.40 Hz), 4.59 (d, 1H, *J* = 12.40 Hz), 3.82 (s, 3H). $^{13}C\{^{1}H\}$ (125MHz, $CDCl_3$) δ (ppm): 172.7, 168.9, 167.3, 164.6, 137.0, 136.9, 135.1, 134.3, 133.3, 132.2, 130.4, 129.8, 129.2, 128.9, 128.8, 128.7, 128.3, 128.2, 127.6, 127.4, 125.3, 124.7, 75.4, 66.3, 53.3, 47.9, 43.9. HRMS (MALDI) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{25}N_2O_5Cl_2^+$ 599.1135, found 599.1158.

Methyl 1-benzamido-8-oxo-6-phenyl-2,3-bis(4-(trifluoromethyl)phenyl)-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4f). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (12.5 mg, 25%). 5 days reaction time. Mp: 107-108 °C. FT-IR (ZnSe, cm^{-1}): 2926, 1810, 1739, 1633, 1323, 1119, 1066, 703. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.10 (d, 2H, *J* = 7.30Hz), 7.71-7.68 (m, 4H), 7.63 (d, 2H, *J* = 7.20 Hz), 7.59-7.51 (m, 7H), 7.43 (t, 2H, *J* = 7.65 Hz), 7.30 (d, 2H, *J* = 8.00Hz), 5.26 (d, 1H, *J* = 12.50 Hz), 4.72 (d, 1H, *J* = 12.50 Hz), 3.83 (s, 3H). $^{13}C\{^{1}H\}$ (125MHz, $CDCl_3$) δ (ppm): 172.7, 168.8, 167.2, 164.8, 139.0, 138.9, 134.4, 132.9, 132.3, 130.5 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.0 (q, $J_{C\text{-}F}$ = 32.1 Hz), 129.3, 129.0, 128.9, 127.5, 127.1, 126.2 (q, $J_{C\text{-}F}$ = 2,5 Hz), 125.4 (q, $J_{C\text{-}F}$ = 3,8 Hz), 124.5, 124.1 (q, $J_{C\text{-}F}$ = 270.4 Hz), 123.8 (q, $J_{C\text{-}F}$ = 270.6 Hz), 75.4, 66.5, 53.4, 47.9, 44.0. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{24}F_6N_2NaO_5^+$689.1482, found 689.1508.

Methyl 1-benzamido-2,3-bis(4-bromophenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4g). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (38.1 mg, 37%). 5 days reaction time. Mp: 89.0-90.0 °C. FT-IR (ZnSe, cm^{-1}): 2917, 1810, 1748, 1633, 1464, 1075, 694. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.07 (d, 2H, *J* = 7.55Hz), 7.69-7.65(m,3H) 7.59 (s, 1H), 7.57-7.51 (m, 3H), 7.45-7.39 (m, 8H), 7.04 (d, 2H, *J* = 8.05 Hz), 5.08 (d, 1H, *J* = 12.55 Hz), 4.55 (d, 1H, *J* = 12.60 Hz), 3.81 (s, 3H). $^{13}C\{^{1}H\}$ (125MHz, $CDCl_3$) δ (ppm): 172.8, 169.0, 167.2, 164.4, 134.2, 134.0, 133.9, 133.1, 132.3, 132.2, 131.6, 130.3, 129.2, 128.8, 128.8, 128.7, 127.1, 124.6, 122.5, 122.1, 75.4, 66.2, 53.3, 47.8, 43.8. HRMS (MALDI) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{25}Br_2N_2O_5^+$687.0125, found 687.0134.

Methyl 1-benzamido-2,3-bis(4-methoxyphenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4h). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (26.6 mg, 60%). 5 days reaction time. Mp: 185.5-186.1 °C. FT-IR (ZnSe, cm^{-1}): 2908, 1810, 1748, 1642, 1518, 1252, 685. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.06 (d, 2H, *J* = 8.00Hz), 7.66-7.62 (m, 3H), 7.52-7.45 (m, 6H), 7.41 (t, 2H, *J* = 7.45 Hz), 7.12 (d, 2H, *J* = 8.35 Hz), 6.82-6.78 (m, 4H), 5.07 (d, 1H, *J* = 12.45 Hz), 4.57 (d, 1H, *J* = 12.30 Hz), 3.81 (s, 3H), 3.74-3.73 (m, 6H). $^{13}C\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 173.4, 169.4, 167.1, 163.7, 159.4, 159.3, 133.8, 133.5, 131.9, 129.8, 129.1, 128.7, 128.6, 128.4, 127.2, 127.0, 125.1, 114.4, 113.9, 75.9, 66.2, 55.3, 55.3, 48.2, 43.9. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{30}N_2O_7Na^+$ 613.1945, found 613.1964.

Methyl 1-benzamido-2,3-bis(3-methoxyphenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4i). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (10 mg, 18%). 5 days reaction time. Mp: 179.3-179.8 °C. FT-IR (ZnSe, cm^{-1}): 2917, 1810, 1739, 1633, 1287, 685. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.06 (d, 2H, *J* = 7.35Hz), 7.65-7.63 (m, 3H), 7.54-7.47 (m, 4H), 7.41 (t, 2H, *J* = 7.40 Hz), 7.22-7.16 (m, 2H), 7.12 (s, 2H), 6.79-6.75 (m, 3H), 6.71 (s, 1H), 5.09 (d, 1H, *J* = 12.40 Hz), 4.61 (d, 1H, *J* = 12.35 Hz), 3.81 (s, 3H), 3.73(s, 3H), 3.69 (m, 6H). $^{13}C\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 173.3, 169.2, 167.1, 164.0, 159.9, 159.7, 137.1, 136.6, 133.9, 133.5, 132.0, 130.1, 129.5, 129.1, 128.9,128.7, 127.6, 127.2, 125.0, 120.9, 119.3, 114.3, 113.7, 112.9, 75.8, 66.3, 55.3, 55.2, 53.1, 48.2, 44.5. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{35}H_{30}N_2O_7Na^+$ 613.1945, found 613.1959.

Methyl 1-benzamido-2,3-bis(3,4-dimethoxyphenyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4j). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (14.6 mg, 30%). 5 days reaction time. Mp: 172.9-173.8 °C. FT-IR (ZnSe, cm^{-1}): 2925, 1819, 1739, 1509, 1243, 1022, 694. ^1H (500 MHz, $CDCl_3$) δ (ppm): 8.06 (d, 2H, *J* = 7.35Hz), 7.67-7.62 (m, 3H), 7.54-7.49 (m, 3H), 7.46 (s, 1H), 7.41 (t, 2H, *J* = 7.70 Hz), 7.16 (s, 1H), 6.99 (d, 1H, *J* = 8.10 Hz), 6.78-6.75 (m, 3H), 6.71 (s, 1H), 5.05 (d, 1H, *J* = 12.45 Hz), 4.52 (d, 1H, *J* = 12.45 Hz), 3.81-3.79 (m, 12H), 3.72 (s, 3H). $^{13}C\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 173.3, 169.3, 167.0, 163.8, 149.3, 149.0, 148.9, 148.8, 133.9, 132.1, 129.1, 128.8, 128.6, 127.7, 127.2, 125.0, 120.5, 119.7, 112.0, 111.4, 110.9, 110.1, 76.1, 66.1, 55.9, 55.9, 53.1, 48.8, 44.5. HRMS (MALDI) *m/z*: $[M+Na]^+$ calcd for $C_{37}H_{34}N_2O_9Na^+$ 673.2157, found 673.2132.

(3-benzamido-3-(methoxycarbonyl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1,2-diyl)bis(4,1-phenylene) diacetate (4k). The product was prepared according to the Condition B

and obtained after flash chromatography in dichloromethane as a white solid (29.1 mg, 60%). 5 days reaction time. Mp: 186-187.5 °C. FT-IR (ZnSe, cm^{-1}): 2917, 1748, 1642, 1500, 1190, 712. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.07 (d, 2H, *J* = 7.15Hz), 7.67-7.62 (m, 3H), 7.55-7.47 (m, 6H), 7.41 (t, 2H, *J* = 7.65 Hz), 7.20 (d, 2H, *J* = 8.35 Hz), 7.02-7.00 (m, 4H), 5.15 (d, 1H, *J* = 12.50 Hz), 4.61 (d, 1H, *J* = 12.45 Hz), 3.81 (s, 3H), 2.25-2.24 (m, 6H). ^{13}C $\{^{1}H\}$ (125MHz, $CDCl_3$) δ (ppm): 172.9, 169.3, 169.2, 167.0, 164.1, 150.5, 133.9, 133.2, 132.4, 132.3, 131.9, 129.6, 129.0, 128.7, 128.6, 128.2, 127.0, 124.7, 122.1, 121.4, 75.5, 66.2, 53.1, 47.8, 43.9, 21.1, 21.1. HRMS (MALDI) *m/z*: $[M+H]^+$ calcd for $C_{37}H_{31}N_2O_9^+$ 647.2024, found 647.2023.

Methyl 1-benzamido-2,3-di(furan-2-yl)-8-oxo-6-phenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4l). The product was prepared according to the Conditions B and obtained after flash chromatography in dichloromethane as a yellow oil (30 mg, 78%). 5 days reaction time. Mp: 186-187.5 °C. FT-IR (ZnSe, cm^{-1}): 3406, 2948, 1817, 1751, 1633, 1509, 1483, 1293, 875, 698. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.04 (dd, 2H, *J* = 8.30, 1.15 Hz), 7.73 (dd, 2H, *J* = 8.10, 1.10 Hz), 7.63 (tt, 1H, *J* = 7.45, 1.25 Hz), 7.56 (s, 1H), 7.54-7.50 (m, 3H), 7.46-7.41 (m, 4H), 7.33 (dt, 2H, *J* = 14.50, 1.7 Hz), 6.52 (s, 1H), 6.5 (s, 1H), 4.74 (d, 1H, J = 12.1 Hz), 4.15 (d, 1H, J = 12.1 Hz), 3.81 (s, 3H). ^{13}C $\{^{1}H\}$ (125MHz, $CDCl_3$) δ (ppm): 173.2, 169.0, 167.1, 163.9, 143.9, 143.4, 141.1, 140.9, 134.0, 132.2, 129.1, 128.8, 128.7, 127.2, 120.5, 110.9, 109.8, 75.6, 65.8, 53.1, 42.5, 38.8. HRMS (MALDI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{23}N_2O_7^+$ 511.1500, found 511.1527.

Ethyl 1-benzamido-8-oxo-2,3,6-triphenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4m). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a yellow solid (20 mg, 47%). 5 days reaction time. Mp: 88.9-90.6 °C. FT-IR (ZnSe, cm^{-1}): 3395, 1810, 1633, 1473, 1287, 694. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.08 (d, 2H, J = 7.55Hz), 7.66-7.62 (m, 3H), 7.58-7.55 (m, 2H), 7.53-7.52 (m, 1H), 7.40 (t, 2H, J = 7.55 Hz), 7.30-7,21 (m, 7H), 7.18 (d, 2H, J = 7.25 Hz), 5.17 (d, 1H, J = 12.40 Hz), 4.71 (d, 1H, J = 12.35 Hz), 4.30-4.25 (m, 2H), 1.28 (t, 3H, J = 7.15 Hz). ^{13}C $\{^{1}H\}$ (125MHz, $CDCl_3$) δ (ppm): 173.2, 168.5, 167.0, 164.0, 135.6, 135.1, 133.9, 133.7, 131.9, 129.1, 129.0, 128.8, 128.7, 128.4, 128.1, 127.9, 127.1, 127.0, 125.1, 75.7, 66.3, 62.2, 47.9, 44.3, 14.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{29}N_2O_5^+$ 545.2071, found 545.2052.

Methyl 1-benzamido-8-oxo-2,3,6-triphenyl-7-oxa-5-azaspiro[3.4]oct-5-ene-1-carboxylate (4n). The product was prepared according to the Condition B and obtained after flash chromatography in dichloromethane as a white solid (17.6 mg, 44%). 3 days reaction time. Mp:

177,2-178,2 °C. FT-IR (ZnSe, cm^{-1}): 2908, 1792, 1721, 1075, 676. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 8.08 (d, 2H, *J* = 7.25 Hz), 7.67- 7.62 (m, 3H), 7.57-7.52 (m, 5H), 7.51-7.48 (m, 1H), 7.42- 7.39 (m, 2H), 7.41 (t, 2H, *J* = 7.65 Hz), 7.31- 7.22 (m, 7H), 7.18 (d, 2H, *J* = 7.55 Hz), 5.17 (d, 1H, *J* = 12.45 Hz), 4.70 (d, 1H, *J* = 12.45 Hz). ^{13}C {^{1}H} (125MHz, $CDCl_3$) δ (ppm): 173.3, 169.3, 167.0, 164.0, 135.5, 135.0, 133.9, 133.5, 131.9, 129.1, 129.0, 128.8, 128.7, 128.7, 128.4, 128.1, 127.9, 127.2, 127.0, 125.0, 75.8, 66.3, 48.1, 44.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{24}D_3N_2O_5^+$ 534.2103, found 534.2115.

General procedures for the Synthesis of compounds 5ai-5aiii

After the procedure described in Condition B, was added, in the same pot, 1 mL of dichloromethane, 10 mol% of CSA and 1.1 equivalent of nucleophile. The vial was sealed with parafilm and stirred at room temperature for 24 h. After the reaction was complete (as judge by TLC analysis) and concentrated in vacuo. It is worth mentioning that all equivalents in this step were calculated based on the starting azlactone of previous procedure (Condition B).

1,2-bis(benzamido)-2-(octylcarbamoyl)-3,4-diphenylcyclobutane-1-carboxylic acid (5a-i). The product obtained after flash chromatography in dichloromethane as a yellow solid (21.0 mg, 44%). 24 hours reaction time. Mp: 57.4-57.7°C. FT-IR (ZnSe, cm^{-1}): 3351, 2917, 1704, 1650, 1518, 685. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 7.65 (d, 2H, *J* = 7.25 Hz), 7.55 (d, 2H, *J* = 7.55 Hz), 7.45-7.38 (m, 4H), 7.37-7.34 (m, 10H), 7.26-7.23 (m, 2H), 6.94 (s, 1H), 6.58 (s, 1H), 5.88 (d, 1H, *J* = 9.80 Hz), 4.26 (d, 1H, *J* = 9.80 Hz), 3.68 (t, 2H, *J* = 7.35 Hz), 1.67-1.64 (m, 2H), 1.30-1.26 (m, 10H), 0.88 (t, 3H, 6.65 Hz). ^{13}C {^{1}H} (125MHz, $CDCl_3$) δ (ppm): 176.3, 173.1, 168. 8, 168.3, 136.1, 132.2, 132.1, 129.0, 128.7, 128.6, 128.2, 128.1, 128.0, 127.4, 127.2, 126.9, 65.6, 63.8, 48.0, 46.5, 39.6, 31.9, 29.3, 29.2, 27.7, 27.0, 22.8, 14.2. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{40}H_{43}N_3NaO_5^+$ 668.3095, found 668.3087.

1,2-bis(benzamido)-2-(benzylcarbamoyl)-3,4-diphenylcyclobutane-1-carboxylic acid (5a-ii). The product was obtained after flash chromatography in 30% of ethyl acetate in hexane as a yellow solid (24.0 mg, 51%). 24 hours reaction time. Mp: 140.0-140.3°C. FT-IR (ZnSe, cm^{-1}): 3359, 2917, 1712, 1650, 1482, 1279, 694. ^{1}H (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, 2H, *J* = 7.10 Hz), 7.48-7.43 (m, 3H), 7.41-7.34 (m, 11H), 7.29-7.22 (m, 6H), 7.21-7.18 (m, 2H), 7.05 (d, 2H, *J* = 7.15 Hz), 6.91 (s, 1H), 6.58 (s, 1H), 5.79 (d, 1H, *J* = 9.55 Hz), 4.87 (d, 2H, *J* = 3.85 Hz), 4.06 (d, 1H, *J* = 9.90 Hz). ^{13}C {^{1}H} (125MHz, $CDCl_3$) δ (ppm): 175.4, 172.6, 172.4, 168.6, 168.2, 135.5, 135.4, 134.3, 133.3, 132.8, 132.1, 132.0, 129.0, 128.9, 128.8, 128.6, 128.6, 128.6, 128.1, 128.0, 127.8, 127.6, 127.1,

126.8, 65.5, 63.6, 47.6, 46.8, 42.7. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{39}H_{33}N_3NaO_5^+$ 646.2312, found 646.2327.

1,2-bis(benzamido)-2-(butylcarbamoyl)-3,4-diphenylcyclobutane-1-carboxylic acid (5a-iii). The product was obtained after flash chromatography in dichloromethane as a yellow solid (16.0 mg, 36%). 24 hours reaction time. Mp: 184.4-185.3°C. FT-IR (ZnSe, cm^{-1}): 3351, 2908, 1704, 1642, 1509, 1473, 685. ^1H (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, 2H, *J* = 7.70 Hz), 7.55 (d, 2H, *J* = 7.40 Hz), 7.46-7.39 (m, 4H), 7.37-7.29 (m, 10H), 7.27-7.24 (m, 2H), 6.92 (s, 1H), 6.57 (s, 1H), 5.87 (d, 1H, *J* = 9.4 Hz), 4.26 (d, 1H, *J* = 10.1 Hz), 3.68 (t, 2H, *J* = 7.00 Hz), 1.66-1.62 (m, 2H), 1.36-1.32 (m, 2H), 0.92 (t, 3H, *J* = 7.30 Hz). ^{13}C $\{^1H\}$ (125MHz, $CDCl_3$) δ (ppm): 175.4, 172.6, 172.4, 168.6, 168.2, 135.5, 135.4, 134.3, 133.3, 132.8, 132.1, 132.0, 129.0, 128.9, 128.8, 128.6, 128.6, 128.6, 128.1, 128.0, 127.8, 127.6, 127.1, 126.8, 65.5, 63.6, 47.6, 46.8, 42.7. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{36}H_{35}N_3NaO_5^+$ 612.2469, found 612.2487.

Supporting Information Statement

General methods, copies of ^1H NMR, ^{13}C NMR, IR spectra for all compounds, X-ray crystallography data, Cartesian coordinates for all stationary points on the potential energy surface.

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Notes
The authors declare no competing financial interest.

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REFERENCES

1. Hu, J.-L., Feng, L.-W., Wang, L., Xie, Z., Tang, Y., Li, X. Enantioselective Construction of Cyclobutanes: A New and Concise Approach to the Total Synthesis of (+)-Piperarborenine B. *J. Am. Chem. Soc*., **2016**, 138, 13151.

2. Miller, Z. D., Lee, B. J., Yoon, T. P. Enantioselective Crossed Photocycloadditions of Styrenic Olefins by Lewis Acid Catalyzed Triplet Sensitization. *Angew. Chem. Int. Ed.*, **2017**, 56, 11891.

3. Yao, X., Conner, M. L., Kevin, B. M. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2+2] Cycloadditions. *Angew. Chem. Int. Ed.*, **2015**, 54, 11918.

4. Chi, Y.-M., Nakamura, M., Yoshizawa, T., Zhao, X.-Y., Yan, W.-M., Hashimoto, F., Kinjo, J., Nohara, T., Sakurada, S. Antinociceptive Activities of α-Truxillic Acid and β-Truxinic Acid Derivatives. *Biol. Pharm. Bull.*, **2005**, 28, 1776.

5. Narayanam, J. M. R., Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.*, **2011**, 40, 102.

6. Chi, Y.-M., Nakamura, M., Zhao, X.-Y., Yoshizawa, T., Yan, W.-M., Hashimoto, F., Kinjo, J., Nohara, T., Sakurada, S. Anti-inflammatory Activity of 4,4′-Dihydroxy-α-truxillic Acid. *Biol. Pharm. Bull.*, **2006**, 29, 580.

7. Berger, W. T., Ralph, B. P., Kaczocha, M., Sun, J., Balius, T. E., Rizzo, R. C., Haj-Dahmane, S., Ojima, I., Deutsch, D. G. Targeting Fatty Acid Binding Protein (FABP) Anandamide Transporters – A Novel Strategy for Development of Anti-Inflammatory and Anti-Nociceptive Drugs. *PLOS ONE*, **2012**, 7, e50968.

8. a) Poplata, S., Tröster, A., Zou, Y.-Q., Bach, T. Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions. *Chem. Rev.*, **2016**, 116, 9748, b) Shaw, M.H., Twilton, J., MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.*, **2016**, 81, 6898.

9. Kärkäs,M. D., Porco J. A., Stephenson, C. R. J. Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis. *Chem. Rev.,* **2016**, 116, 9683.

10. Pinheiro, D. L. J., Ávila, E. P., Amarante, G. W. A Practicable Synthesis of Oxazol-5(4H)-ones Through Hydrogenation: Scope and Applications. *ChemistrySelect*, **2016**, 1, 2960.

11. Melhado, A. D., Amarante, G. W., Wang, Z. J., Luparia M., Toste, F. D. Gold(I)-Catalyzed Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition and Mannich Reactions of Azlactones. *J. Am. Chem. Soc.*, **2011**, 133, 3517.

12. Ávila, E. P., Justo, R. M. S., Gonçalves, V. P., Pereira, A. A., Diniz, R., Amarante, G. W. Chiral Brønsted Acid-Catalyzed Stereoselective Mannich-Type Reaction of Azlactones with Aldimines. *J. Org. Chem.*, **2015**, 80, 590.

13. Pereira, A. A., de Castro, P. P., de Mello, A. C., Ferreira, B. R. V., Eberlin, M. N., Amarante, G. W. Brønsted acid catalyzed azlactone ring opening by nucleophiles. *Tetrahedron*, **2014**, 70, 3271.

14. Pinheiro, D. L. J., Ávila, E. P., Batista, G. M. F., Amarante, G. W. Chemoselective Reduction of Azlactones Using Schwartz's Reagent. *J. Org. Chem.*, **2017**, 82, 5981.

15. Liu, Q., Li, N., Yuan, Y., Lu, H., Wu, X., Zhou, C., He, M., Su, H., Zhang, M., Wang, J., Wang, B., Wang, Y., Ma, D., Ye, Y., Weiss, H.-C., Gesing, E. R. F., Liao, J., Wang, M.-W. Cyclobutane Derivatives As Novel Nonpeptidic Small Molecule Agonists of Glucagon-Like Peptide-1 Receptor. *J. Med. Chem.*, **2012**, 55, 250.

16. García-Montero, A., Rodriguez, A. M., Juan, A., Velders, A. H., Denisi, A., Jiménez-Osés, G., Gómez-Bengoa, E., Cativiela, C., Gómez, M. V., Urriolabeitia, E. P. Metal-Free [2 + 2]-Photocycloaddition of (Z)-4-Aryliden-5(4H)-Oxazolones as Straightforward Synthesis of 1,3-Diaminotruxillic Acid Precursors: Synthetic Scope and Mechanistic Studies. *ACS Sustainable Chem. Eng.*, **2017**, 5, 8370.

17. Elena, S., Alberto, J., Angel, G. M., Tatiana, S., Francisco, J. M., Carlos, C., Victoria, G. M., Urriolabeitia, E. P. Stereoselective Synthesis of 1,3-Diaminotruxillic Acid Derivatives: An Advantageous Combination of C-H-ortho-Palladation and On-Flow [2+2]-Photocycloaddition in Microreactors. *Chem. Eur. J.*, **2016**, 22, 144.

18. 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, 5322.

19. Stoermer, R., Laage, E. Über die siebente Säure der Truxillsäuregruppe, die Neo-truxinsäure. (V). *Ber. Dtsch. Chem. Ges.*, **1921**, 54, 96.

20. Stoermer, R., Scholtz, F. Über die 6. Säure der Truxillsäure-Gruppe, ζ-Truxinsäure (Zetruxinsäure). (IV.). *Ber. Dtsch. Chem. Ges.*, **1921**, 54, 85.

21. de Castro, P. P., Carpanez, A. G., Amarante, G. W. Azlactone Reaction Developments. *Chem. Eur. J.*, **2016**, 22, 10294.

22. de Castro, P. P., dos Santos, I. F., Amarante, G. W. Brønsted Acid Catalyzed Peptide Synthesis through Azlactone Rings. *Curr. Org. Synth.,* **2016**, 13, 440.

23. Srivastava, V., Singh, P. P. Eosin Y catalysed photoredox synthesis: a review. *RSC Adv.,* **2017**, 7, 31377.

24. Sheldrick, G. M. SHELXT – Integrated space-group and crystal-structure determination. *Acta Cryst.*, **2015**, A71, 3–8.

25. Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.*, **2015**, C71, 3–8.

26. Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K., Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.*, **2009**, 42, 339–341.

27. Farrugia, L. J., WinGX and ORTEP for windows: an update, *J. Appl. Crystallogr.,* **2012**, 45, 849–854.

28. Blanco-Lomas, M., Funes-Ardoiz, I., Campos, P. J., Sampedro D. Oxazolone-Based Photoswitches: Synthesis and Properties. *Eur. J. Org. Chem.,* **2013**, 6611.

29. Rao, A. M. L. P., Rao, A. S., Babu, M. S., Rao, M. K., Triphenylphosphine (PPh3) Catalyzed Erlenmeyer Reaction for Azlactones under Solvent-free Conditions. *J. Heterocyclic Chem.*, **2017**, 54, 429.

30. Dürüst, Y., Sagurlı, A., Fronczek, F. R. Regioselective 1,3-dipolar cycloaddition of phenanthrolinium *N*-ylides to substituted arylidene oxazolones. *Mol Divers*, **2011**, 15, 799.