



Two photons are better than one: continuous flow synthesis of β -lactones through a doubly photochemically-activated Paternò-Büchi reaction

Federica Minuto¹ · Emanuele Farinini² · Serena De Negri¹ · Riccardo Leardi² · Davide Ravelli³ · Pavlo Solokha¹ · Andrea Basso¹

Received: 16 October 2023 / Accepted: 27 November 2023 / Published online: 15 December 2023
© The Author(s) 2023

Abstract

In this paper we report a [2 + 2] cycloaddition reaction between ketenes and benzils, characterized by an unusual double photochemical activation triggered by visible light. Employment of a flow system and optimization of reaction conditions through Design of Experiments resulted in moderate to good yields of the corresponding β -lactones. A thorough computational analysis allowed to elucidate the mechanism of the reaction and justify the observed diastereoselectivity. The reaction was also successfully tested with mixed benzils, showing complete regioselectivity.

Keywords Diazoketones · β -Lactones · Flow Chemistry · Design of Experiments · Paternò-Büchi reaction · Visible light

Introduction

The synthesis of four-membered rings is a continuous challenge for synthetic chemists since these scaffolds are versatile building blocks in drug discovery campaigns. In particular, β -lactones and β -lactams attracted great interest in the field of medicinal chemistry and chemical biology, thanks to the intrinsic reactivity of the strained four-membered heterocycle [1]. Since 1883, the reactivity and the possible transformations of β -lactones have been the object of intense investigations [2], along with their synthesis on the route to the preparation of natural products [3–5]. Nowadays, the most common synthetic methodologies toward these scaffolds employ ketenes as starting materials. Despite their intrinsic reactivity and instability [6], many examples describing the cycloaddition between ketenes and carbonyl compounds to deliver β -lactones have been reported in the

literature. Starting from stable ketenes [7], it is possible to obtain the desired products employing *N*-heterocyclic carbenes (NHCs; see Scheme 1a) [8–10], phosphines [11, 12] or Lewis acid–Lewis base (LA*–LB*) bifunctional catalysts [13], to activate the carbonyl group at its ground state.

A useful strategy for the *in situ* generation of ketenes is represented by the photoinduced Wolff rearrangement of α -diazoketones. Interestingly, the photogeneration of ketenes does not require any additional species, such as metal catalysts or bases, or harsh conditions such as heating, leading to a simplification of the reaction system, in terms of costs and sustainability. Recently, we demonstrated that α -alkyl and α -aryldiazoketones can undergo a Wolff rearrangement under visible light irradiation [14]. The resulting ketene intermediates can be involved in multicomponent processes, such as the Ketene Three-Component Reaction (K-3CR) [15, 16] and its silylative version (SK-3CR) [17], as well as a three-component version of the Staudinger Reaction (K-3CSR) [18]. Photogenerated ketenes have been also employed in [2 + *n*] cycloaddition processes, giving access to a wide number of new cyclic architectures [19].

Considering all these synthetic pathways, we have identified a missed one that could be realized by taking advantage of the same visible light used to generate such synthetic intermediates. In fact, ketenes could react as alkenes (2π reaction partners) in a Paternò-Büchi reaction [20, 21] with carbonyl derivatives, still leading to four-membered β -lactones, but

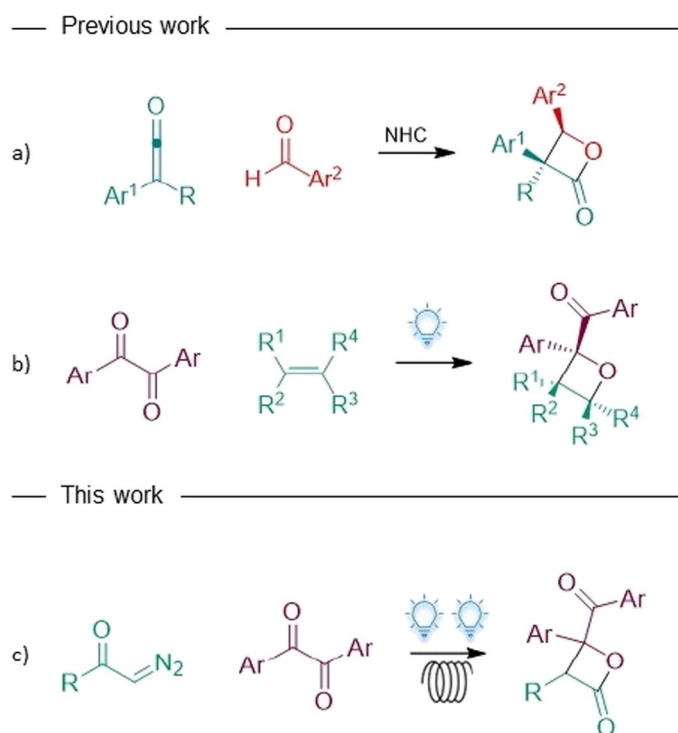
✉ Andrea Basso
andrea.basso@unige.it

¹ Università degli Studi di Genova, Dipartimento di Chimica e Chimica Industriale, Genoa, Italy

² Università degli Studi di Genova, Dipartimento di Farmacia, Genoa, Italy

³ Università degli Studi di Pavia, Dipartimento di Chimica, PhotoGreen Lab, Pavia, Italy

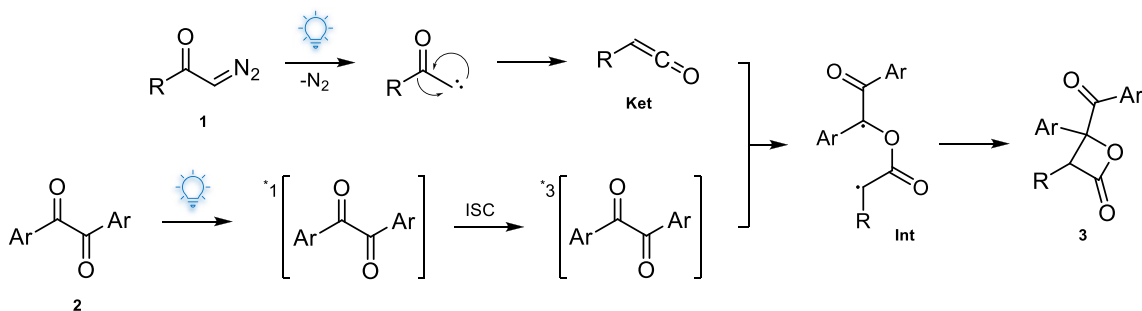
Scheme 1 a) General synthesis of β -lactones through NHC catalysis from stable ketenes; b) General Paternò-Büchi Reaction between olefins and benzils; c) General doubly photochemically-activated Paternò-Büchi Reaction between α -diazoketones and benzils (this work)



through a different approach, in which the carbonyl reactant is activated by light and not upon acid catalysis. This hypothesis is supported by our recent work (Scheme 1b), wherein we have demonstrated that benzil-type carbonyls can be excited by visible light and react via the triplet state in [2+2]-cycloadditions with alkenes [22–24]. Thus, based on our experience, we decided to combine the photogeneration of ketenes with a catalyst-free [2+2] photocycloaddition with benzils (Scheme 1c). As depicted in Scheme 2, we postulate that benzils (**2**) could react also with ketenes (**Ket**, formed upon irradiation of diazoketones **1**), with the initial formation of a 1,4-diradical intermediate (**Int**), that ultimately delivers the desired cycloadduct **3**. Compared to what already reported in the literature, the process described in this article displays an unusual double photochemical activation of both starting materials.

Results and discussion

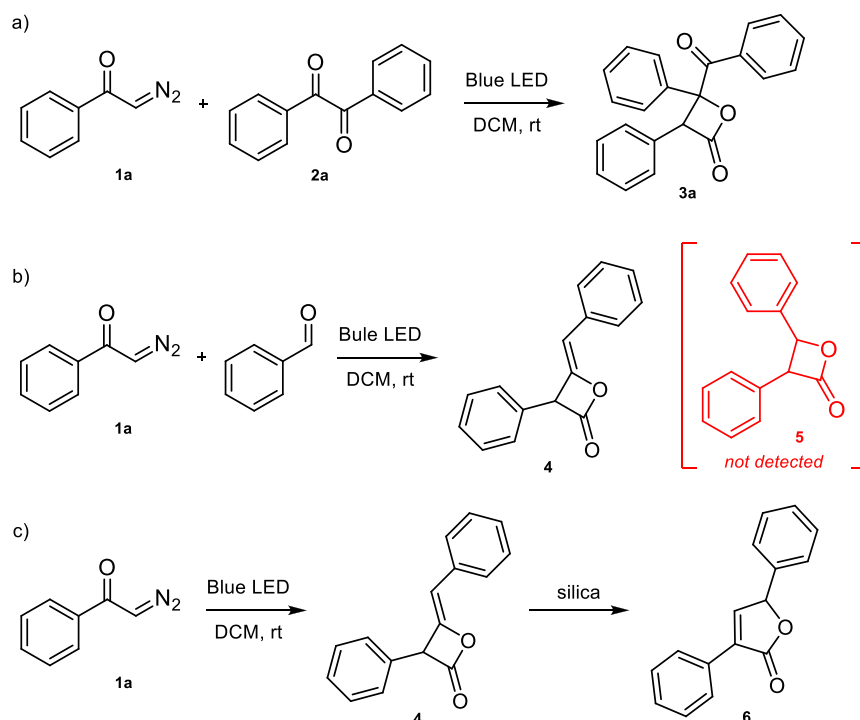
We started our investigation irradiating with blue LEDs a degassed dichloromethane (DCM) solution of phenyl diazoketone **1a** and benzil **2a** (Scheme 3a) until disappearance of the diazoketone and analyzed the crude mixture by GC–MS and NMR. We were pleased to find that both analyses indicated the presence of two products (major:minor 1:0.4) compatible with β -lactone **3a**, albeit in small amounts. Upon purification of the crude, two diastereomeric β -lactones **3a** were isolated in an overall 30% yield and fully characterized, confirming our hypothesis. In a control experiment, a solution of **1a** and **2a** was kept in the dark for 24 h, and the compounds were recovered unreacted, demonstrating the essential role of light



Scheme 2 Proposed mechanism of a general doubly photochemically-activated Paternò-Büchi Reaction between α -diazoketones and benzils (ISC, Intersystem Crossing)

Scheme 3 Preliminary experiments. **a)** Reaction of diazoketone **1a** with benzil **2a** affording β -lactone **3a** (no trace of **4** was detected in the crude NMR).

b) Reaction of diazoketone **1a** with benzaldehyde: NMR of the crude displayed two doublets ($J=2.8$ Hz) at 4.66 and 6.02 ppm consistent with structure **4** (no NMR data available in the literature); tabulated peaks for **5** are: cis (5.35 ppm, d, $J=6.8$ Hz) and 5.89 ppm, d, $J=6.8$ Hz) [27]; trans (4.60 ppm, d, $J=4.4$ Hz and 5.35 ppm, d, $J=4.4$ Hz) [28]. **c)** Dimerization of diazoketone **1a**; postulated compound **4** rearranged to compound **6** [29]



irradiation. To exclude that the photogenerated ketene could react with the carbonyl derivative in the ground state, **2a** was replaced by benzaldehyde and the resulting mixture irradiated until disappearance of the diazoketone. NMR of the crude mixture showed the presence of a new compound, that was postulated to be the ketene dimer **4** [6, 25, 26], while no adduct **5** between ketene and benzaldehyde was observed (Scheme 3b). This result was confirmed by irradiating a solution of the sole diazoketone **1a**, that again afforded the supposed ketene dimer **4** as major product. These results led us to speculate that benzaldehyde, unable to be excited by blue light, remains as spectator in the ketene transformations, while benzil, capable of excitation at this wavelength [22], becomes the preferred reaction partner for the ketene. It is worth mentioning, in fact, that no trace of dimer was detected in the reaction mixture of the first experiment. Attempts to isolate the ketene dimer by flash chromatography failed, as this immediately rearranged to but-2-en-4-olide **6** upon exposure to silica (Scheme 3c).

Reaction optimization in batch and under continuous flow

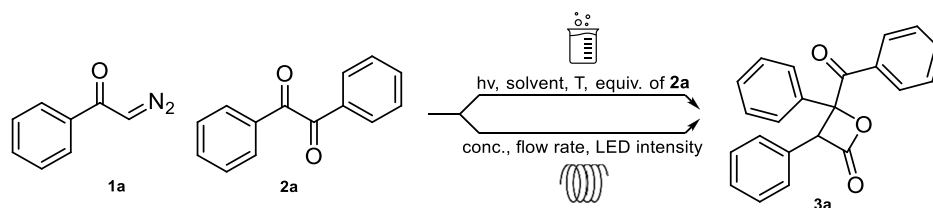
With these preliminary, but promising, results in hand, we decided to optimize the conditions of the reaction between phenyl diazoketone **1a** and benzil **2a**. The choice was made to employ the Design of Experiments (DoE), an efficient chemometric approach that allows extracting high-quality information from a limited number of planned experiments

[30]. This chemometric method, first introduced by Fisher in 1935, is widely recognized and should be applied in all phases of optimization of a given (industrial) chemical process. However, its implementation is not widespread, as it is neither universally adopted, nor consistently exploited. As a matter of fact, in the context of organic synthesis, the literature often includes references to optimization studies using "one variable at a time" (OVAT) approaches [31]. To ensure a proper project design, it is essential to identify all possible variables that can have an effect within the considered system. At the beginning, we studied the reaction in batch, creating an ad hoc D-Optimal Design, and then moved to a continuous flow system realizing a Central Composite Design (Scheme 4).

D-Optimal Design

For the screening design, various factors along with different setting levels were identified, including wavelength [32], solvent, temperature, and equivalents of benzil, all listed in Table 1.

A multi-step experimental design strategy was followed, aiming to achieve the highest yield, determined through a GC–MS analysis using an internal standard (benzyl phenyl sulfide), by selecting the most effective variables and their corresponding levels. For each step, a set of replicates was selected to evaluate any time-related blocking effects due to the experimental session. Based on the profound asymmetry between the conditions, the first experimental plan was meticulously designed to achieve the highest possible



Scheme 4 Study of the reaction between phenyl diazoketone **1a** and benzil **2a** to β -lactone **3a** in two different systems (batch and flow) and the corresponding investigated conditions

Table 1 Variables with the corresponding levels

Var. ID	Variable	Levels					
X1	Wavelength	365 nm	385 nm	405 nm	450 nm*	470 nm	
X2	Temperature	-15 °C	0 °C	rt*			
X3	Solvent	MeCN	DCM*	Et ₂ O	MeOH	THF	HC(OMe) ₃
X4	Equiv. of 2a	1	1.5	2			

*implicit level

degree of orthogonality, effectively minimizing collinearity (Variance Inflation Factor, VIF < 1.89), and facilitating the construction of a regression model (Multiple Linear Regression, MLR).

From the first set of experiments, it was observed that all tested solvents performed worse than DCM, which served as the baseline in the design (implicit level). All the screened reaction media presented a negative coefficient (fully significant; Fig. 1a, see Supplementary Information for more details). Consequently, the second step involved the study of the same factors at the same levels as the previous step, but with the solvent fixed with the best one, DCM (see Table 1). A total of 30 experiments was planned with an experimental matrix designed using the same logic as the previous step to achieve the highest possible degree of orthogonality. From this step, it was found that wavelengths of 365 nm and 385 nm performed worse than the others, the temperature of -15 °C was better than higher temperatures but not significantly, and the number of equivalents had no effect. To get more interpretable results, a second elaboration was performed excluding experiments at 365 nm and 385 nm due to the poor results. It was found that the temperature of -15 °C was significantly better than rt and 0 °C; the wavelengths 470 nm and 405 nm were not significantly better than 450 nm, making them worth studying for the subsequent step.

The third step aimed to study the interactions between the same variables (wavelength, temperature, and equivalents) at the levels reported in Table 2. A few supplementary experiments were performed to assess the interactions among them. From the results, it was observed that irradiation of the reaction mixture in DCM at 470 nm and -15 °C led to the highest yield (45%), and the number of equivalents of

Table 2 Variables with the corresponding levels of the third step

Var. ID	Variable	Levels		
		-1	0	1
X ₁	Wavelength	450 nm		470 nm
X ₂	Temperature	-15 °C		rt
X ₃	Equiv. of 2a	1	1.5	2

benzil had no effect on the system. The interaction between wavelength and temperature, as shown in Fig. 1a, was found to be significant. From the isoresponse (Fig. 1b), it was evident that the effect of the wavelength is absent when working at low temperatures.

Having established the optimal conditions to perform the [2+2] cycloaddition in batch mode, we then moved to investigate the same reaction under continuous flow conditions. The potential for optimizing various processes within such dynamic systems is widely acknowledged [33]. Notably, the in-house apparatus available in our laboratory (see Supplementary Information for a detailed description) had some limitations, forcing us to work at room temperature with irradiation at 450 nm. However, the previous study realized under batch conditions showed that the outcome of the reaction performed at 450 nm and room temperature (highest yield: 37%) was not dramatically different from the outcome performed at 470 nm and -15 °C (45%), highlighting the possibility to operate in our continuous flow system.

Central Composite Design

An initial exploratory experiment was conducted at 450 nm wavelength and room temperature, employing DCM as the

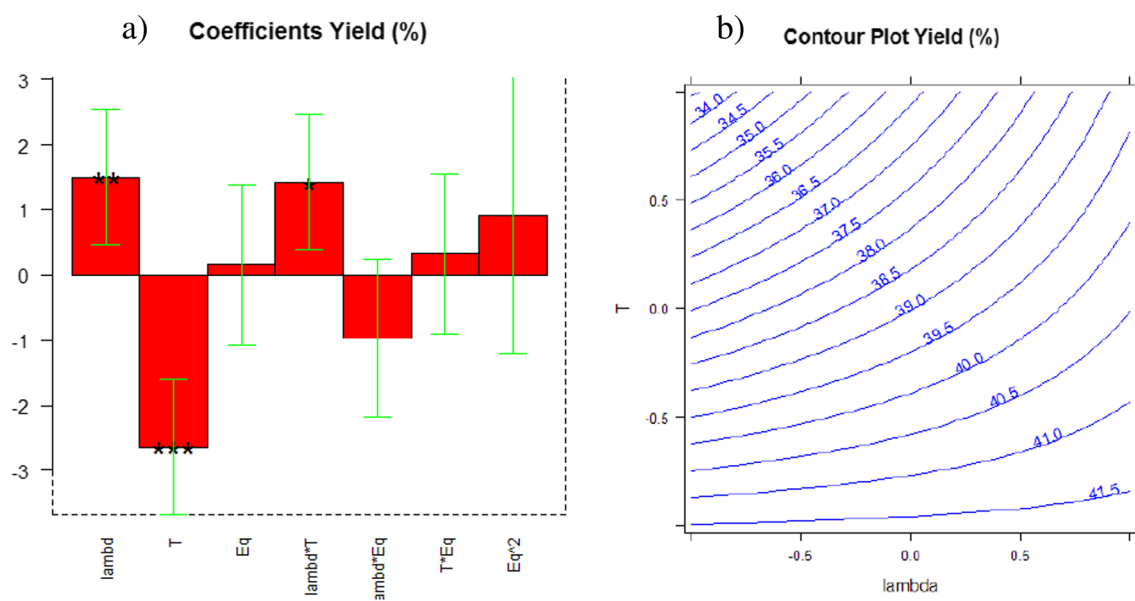


Fig. 1 a) Plot of the coefficients yield (%), interaction between wavelength and temperature; b) Contour plot yield (%) of the response surface of the studied system

solvent. Gratifyingly, a reaction yield comparable to the best one obtained under optimized batch conditions (470 nm at $-15\text{ }^{\circ}\text{C}$) was achieved, showing that the reaction was performing better under continuous flow and justifying our decision of using reaction conditions that did not correspond to the optimum found before.

As a result, a Central Composite Design was subsequently employed. The factors identified were: concentration of the reagents, flow rate, and LED intensity, as delineated in Table 3. In this case, the experimental matrix consisted of 18 experiments and the reaction yields were calculated by NMR integration (see Supplementary Information for more details).

For the regulation of LED intensity, a benchtop power supply and a photodiode connected to a tester were employed. After positioning the setup on the benchtop, the current was adjusted to its maximum for measurement purposes. Subsequently, incremental modifications were made to the applied voltage until the emitted radiant power, as detected by the photodiode, was equal to a predefined value. It is worth noting that a preliminary calibration of the system was required.

The influence of LED intensity was found to be significant in affecting the outcome (Fig. 2a). When irradiating the reaction at 0.73 mA, a reaction yield of 66% was observed. The remaining variables under investigation are indications of system robustness. This is demonstrated by comparable outcomes when conducting the reaction at varying levels of each respective variable. The response surface of the system is illustrated in Fig. 2b.

Reaction scope

Gratified by these results, we then moved to investigate the possibility of using structurally different diazoketones and benzils to obtain analogues of compound **3a**. The reactions were conducted under continuous flow conditions using the optimized conditions previously determined. Various aryl-diazoketones, including heteroaromatic ones, afforded the desired products **3b**, **3c** and **3d**. On the other hand, aliphatic diazoketones failed to afford the desired products (see the case of product **3e**). Concerning 1,2-diketones, we conveniently tested *p*-Br substituted benzil (product **3f**), however, the reaction did not occur in the presence of electron-donating substituents (MeO- and Me₂N-, on the route to products **3g** and **3h**, respectively), possibly because of a preferred π - π^* excited state [34]. In Fig. 3, the structures of the synthesized compounds are reported, together with the yields determined by NMR. In all cases a 1:0.4 mixture of diastereoisomers was obtained, but isolation of the products by column chromatography was often difficult due to the close polarity of the products with unreacted benzil and partial

Table 3 Variables of the system in Central Composite Design

Var. ID	Variable	Levels		
		-1	0	1
X ₁	Concentration (M)	0.02	0.04	0.06
X ₂	Flow rate (mL/h)	0.5	0.75	1
X ₃	LED intensity (mA)	0.36	0.54	0.73

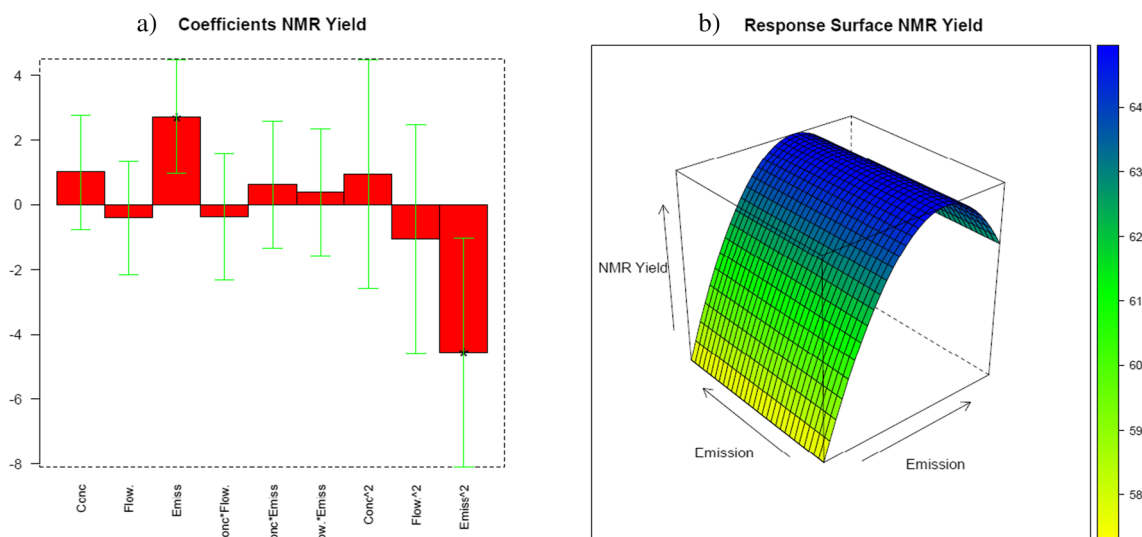


Fig. 2 a) Plot of the coefficients yield (%) obtained from the Central Composite Design; b) Response surface of the studied system

instability of these β -lactones on silica and alumina. The major diastereoisomer of compound **3f** (labelled **3f^{trans}** due to the relative *trans* arrangement between the two aromatic groups directly attached to the lactone skeleton) could be isolated by precipitation in 45% yield, consistent with the value estimated by NMR (60% for the sum of the two diastereoisomers), demonstrating the reliability of the method used. The isolated **3f^{trans}** product was characterized by single crystal X-ray diffraction, that confirmed its relative stereochemistry (Fig. 4). Its structural model (deposited code CSD-2250935) was found in the monoclinic system, space group $P2_1/n$ (N. 14), with refined parameters $a = 6.6352(2)$ Å, $b = 10.7113(3)$ Å, $c = 25.8904(8)$ Å, $\beta = 92.3460(10)^\circ$ and good residual values ($R1 = 4.79\%$ and $wR2 = 12.36\%$).

In order to test the possibility of using mixed benzils, mono 4-methoxy substituted benzil was reacted with phenyldiazoketone **1a**, and, in agreement with the observation that a 4-methoxyphenyl substituent was probably deactivating the adjacent carbonyl group, only regioisomer **3i** was formed, although in moderate yield.

Because of the difficulties encountered in chromatographic isolation of some of the products, to obtain analytically pure samples, in some cases crude mixtures of cycloadducts **3** were subjected to lactone-ring opening with methylamine (Scheme 5). The reaction was complete in less than one hour, and the resulting β -hydroxy amides **7a**, **7b** and **7i** were stable, therefore they could be purified by flash chromatography and fully characterized.

Theoretical studies

To get more insights into the mechanism of the reported transformation, in particular the cycloaddition step, and

possibly rationalize the observed stereochemical course [35], we undertook a computational investigation describing the different steps accompanying the formation of products **3** [36]. In our computational work, we applied density functional theory (DFT) based on the B3LYP functional coupled with the 6-311+G(d,p) basis set to optimize all the relevant structures. Preliminary work was performed in the gas phase, while the solvent effect has been subsequently included through an implicit model (dichloromethane bulk) via single point calculations performed on the geometries previously obtained (see Supplementary Information for further details). We focused our attention on the formation of product **3a** from the model reaction between parent benzil **2a** and the in situ photogenerated ketene **Ket** (from phenyldiazoketone **1a**). According to the definition offered above, the two diastereoisomers have been labelled as **3a^{trans}** and **3a^{cis}**, respectively, to identify the major and minor derivatives formed in this process. As reported in our previous work [22], this type of [2 + 2]-cycloaddition involves the initial formation of a diradical intermediate (**Int**) and the consequent ring closure step (see Scheme 2 above). For this reason, we split our theoretical work in two parts, the first describing the conversion of starting materials into **Int** and the second focusing on the formation of the desired cycloadduct(s) from **Int**. As depicted in Fig. 5, we therefore optimized that structure of **2a** in the ground state and its lowest-lying triplet excited state (**³2a**). According to our computational data, the triplet energy of benzil is *ca.* 48 kcal·mol⁻¹, in good agreement with the literature value of 53.7 kcal·mol⁻¹ [37]. Noteworthy, the main geometric effect related to the population of **³2a** from **2a** consists in a sort of flattening of the overall structure, with the dihedral angle between the two oxo groups moving from *ca.* 117° to 174°.

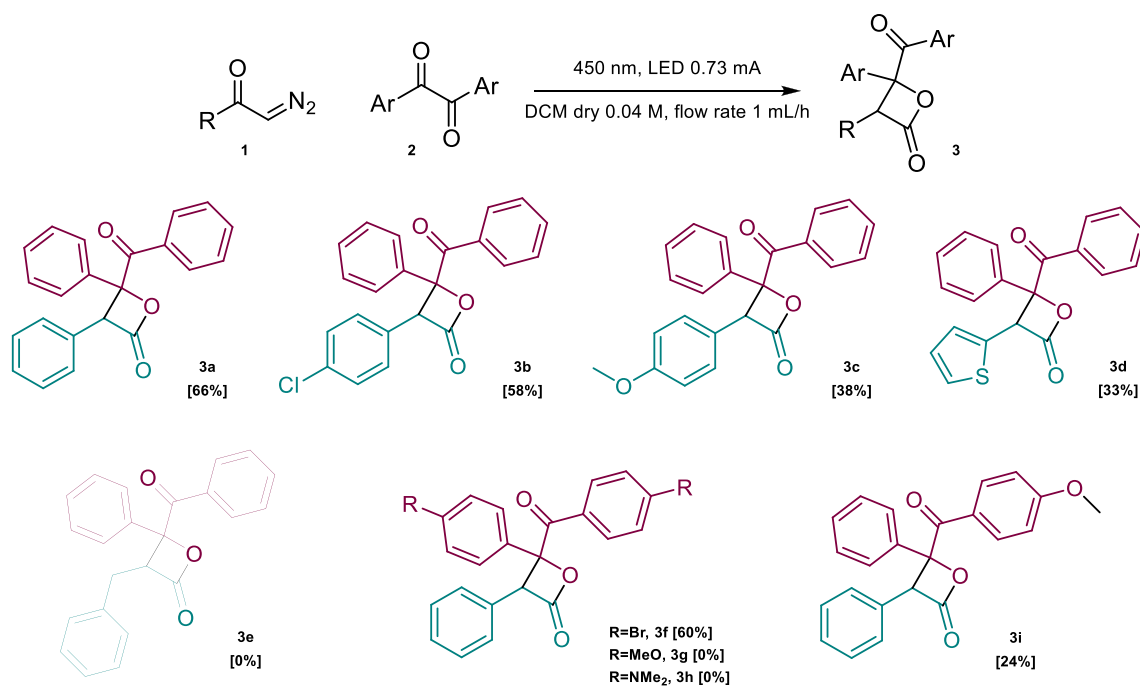


Fig. 3 Scope of the doubly photochemically-activated Paternò-Büchi reaction between various diazoketones **1** and benzils **2** (NMR yields in brackets). Reactions were performed dissolving diazoketones

(0.1 mmol) and benzils (0.1 mmol) in the given solvent (2.5 mL, 0.04 M) and irradiating the resulting solution in a continuous flow system (rate 1 mL/h, see supplementary information for details)

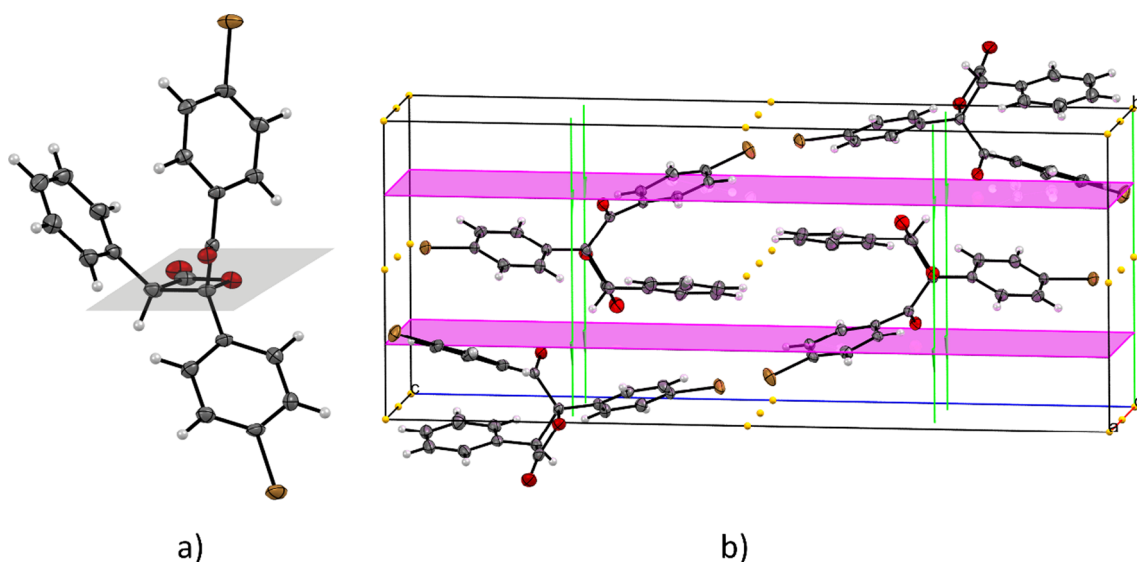
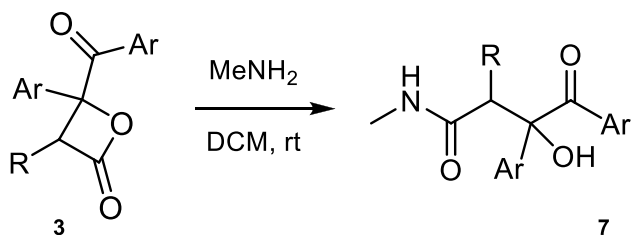


Fig. 4 Structure of the **3f^{trans}** product (major diastereoisomer) as obtained from X-ray analysis. **a)** Distribution of atoms within the molecule (the lactone-ring plane is highlighted in grey). All atoms except hydrogen ones are shown by their thermal displacement ellip-

oids indicated with 50% probability level; **b)** Molecules packing inside the unit cell together with symmetry elements (yellow points: inversion centres; green lines: two-fold screw axes; pink planes: glide planes)

Once formed, triplet benzil **3a** easily reacts with ketene **Ket** through **TS-1** via formation of a new C–O linkage. The ΔG^\ddagger associated with this transition state is only 7.4 kcal·mol⁻¹ and leads to the formation of the 1,4-diradical intermediate

Int in its triplet state (**³Int**), via an overall exergonic process ($\Delta G = -14.4$ kcal·mol⁻¹). The latter species may also evolve into the corresponding open-shell singlet diradical **¹Int** [38], which lies only 1.5 kcal·mol⁻¹ below the triplet



Scheme 5 General lactone-ring opening reaction with methylamine

state. Interestingly, both spin states of **Int** share very similar geometric features, with the moieties originally associated with the ketene and the diketone lying in perpendicular planes. This specific arrangement is probably associated to the minimization of the repulsion between the two unpaired electrons, that lie in almost orthogonal orbitals (see Supplementary Information, Figure S3).

Next, we moved to the second step of our process, focusing on the evolution of the 1,4-diradical intermediate **Int** towards the final cycloadduct **3a**. Given its peculiar geometry, **Int** should allow for the formation of both diastereoisomers of the final cycloadduct, being a common intermediate on the way towards the two stereochemical outputs (**3a^{trans}** and **3a^{cis}**). Since the first step of this Paternò-Büchi process occurs on the triplet manifold surface, we initially optimized the diastereoisomeric transition states describing the formation of the lactone ring via C–C bond formation in the triplet state (tagged **³TS-2**). The corresponding intrinsic reaction coordinate (IRC) profiles are gathered in Fig. 6 (see

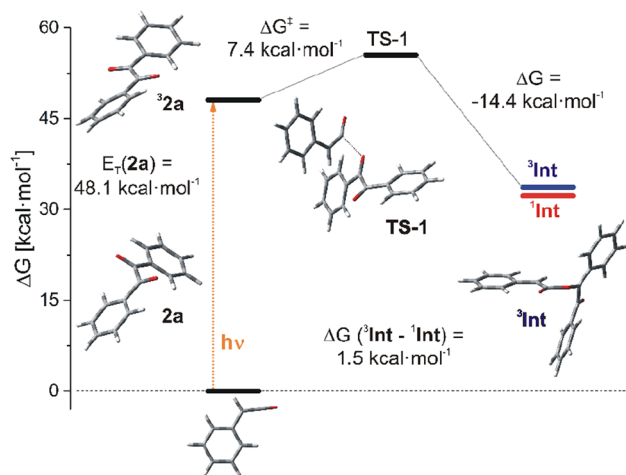


Fig. 5 Reaction profile associated with the model process between **2a** and photogenerated ketene (**Ket**; from **1a**) according to the general mechanism depicted in Scheme 2, as from calculations at the B3LYP/6-311+G(d,p) level of theory in dichloromethane (DCM) bulk

Supplementary Information for more details). As apparent from Fig. 6 and the data gathered in Table S5, the energy of the located transition states is quite high (*ca.* 48–49 kcal·mol⁻¹ above **³Int**) independently from the stereochemical course, although the **³TS-2** describing the *trans* pathway is more stable by *ca.* 1.5 kcal·mol⁻¹ than the corresponding *cis* pathway. We therefore attempted an optimization of the same transition states in the singlet manifold (to locate **¹TS-2**), however, all our efforts were unsuccessful. For this reason and based on the structural similarities observed above for **^{1,3}Int**, we performed single-point calculations in the singlet spin state on selected geometries resulting from the IRC obtained for **³TS-2** (both in the *trans* and *cis* manifold). This allowed us to have an estimate of the reaction profile along the singlet spin state (Fig. 6), which clearly shows that: i) earlier **¹TS-2** are encountered and ii) they lie much lower in energy than the corresponding triplets (*ca.* 13–14 kcal·mol⁻¹ above **¹Int**); also in this case, the *trans* pathway is slightly more stable than the *cis* one by *ca.* 0.9 kcal·mol⁻¹ (see Supplementary Information, Table S5).

Finally, we optimized the structure of the two diastereoisomeric products (**3a^{trans}** and **3a^{cis}**) formed from our model reaction and their structures are reported in Fig. 7. According to our calculations, the *cis* isomer is more stable than the *trans* one by *ca.* 1.8 kcal·mol⁻¹; worth of notice is that both products have a higher energy content with respect to the sum of the starting materials, pointing to an overall endergonic transformation (by *ca.* 6–8 kcal·mol⁻¹, depending on the considered diastereoisomer) [39].

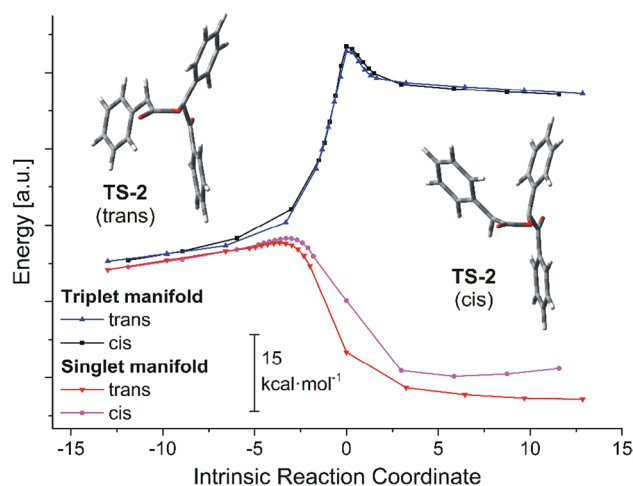
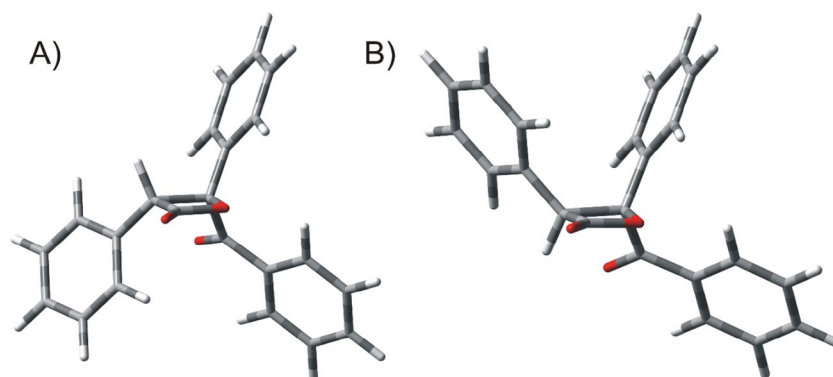


Fig. 6 Reaction profiles describing the formation of cycloadduct **3a** from the 1,4-diradical intermediates (**^{1,3}Int**) depending on the spin manifold and the stereochemical outcome, as from calculations at the B3LYP/6-311+G(d,p) level of theory in dichloromethane (DCM) bulk

Fig. 7 Geometries of the diastereoisomeric products: **a)** **3a^{trans}** (major diastereoisomer) and **b)** and **3a^{cis}** (minor diastereoisomer)



Conclusions

In conclusion, we have reported for the first time a general, visible-light photoinduced Paternò-Büchi-based β -lactones synthesis that involves a double photochemical activation. Optimal conditions have been found both for the batch and the flow mode using a Design of Experiment (DoE) approach. Despite the moderate reaction yield in some cases, the reaction outcome showed an improvement when moving from traditional batch conditions to a flow system. DoE has been rarely exploited in organic synthesis and, at any rate, almost exclusively in batch conditions, leaving the application of such strategy under continuous flow manifold unexplored [40]. This novel procedure is characterized by a great synthetic simplicity and does not require any catalyst or photoinitiator [41–43]. Both symmetrical and mixed benzils could be employed, as well as various aryl diazoketones. Finally, the reaction has been studied also from a computational point of view, suggesting that, after an initial step on the triplet energy surface that leads to a 1,4-diradical intermediate, cyclization of the latter probably occurs on the singlet surface. Indeed, we expect that intersystem crossing from the triplet to the more stable singlet manifold may occur at the 1,4-diradical intermediate level or in the early stages of the cyclization step, where the two surfaces lie near to each other, therefore impacting on the overall stereoselectivity observed [44–46]. Noteworthy, the final β -lactone products are formed as diastereomeric mixtures and the process seems to be under kinetic control, leading to the preferential formation of the less stable “*trans*” isomer.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1007/s41981-023-00297-7>.

Acknowledgements We thank Dr. Luca Capaldo (University of Parma) for fruitful discussion. Calculations were carried out at the CINECA Supercomputer Center (Italy), with computer time granted by ISCR project HP10CAOFN4. A. B. thanks Mrs. Beatrice Massone for her precious collaboration and acknowledges support from Fondazione Compagnia di San Paolo—Bando Trapezio (ID ROL 67533); D.R. acknowledges support from the Ministero dell’Università e della

Ricerca (MUR) and the University of Pavia through the program “Dipartimenti di Eccellenza 2023–2027”.

Funding Open access funding provided by Università degli Studi di Genova within the CRUI-CARE Agreement.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Böttcher T, Sieber SA (2012) β -Lactams and β -lactones as activity-based probes in chemical biology. *Med Chem Comm* 3:408–417. <https://doi.org/10.1039/C2MD00275B>
2. Wang Y, Tennyson RL, Romo D (2004) β -Lactones: intermediates for natural product total synthesis and new transformations. *Heterocycles* 64(1):605–658
3. Pommier A, Pons JM (1993) Recent advances in β -lactone chemistry. *Synth* 1993(05):441–459. <https://doi.org/10.1055/s-1993-25878>
4. Pommier A, Pons JM (1995) The synthesis of natural 2-oxetanones. *Synth* 1995(07):729–744. <https://doi.org/10.1055/s-1995-4011>
5. Lowe C, Vederas JC (1995) Naturally occurring β -lactones: Occurrence, syntheses and properties. *Org Prep Proc Int* 27(3):305–346. <https://doi.org/10.1080/00304949509458466>
6. Tidwell TT (2006) Ketene chemistry after 100 years: ready for a new century. *Eur J Org Chem* 2006(3):563–576. <https://doi.org/10.1002/ejoc.200500452>

- Lv H, Zhang YR, Huang XL, Ye S (2008) Asymmetric Dimerization of Disubstituted Ketenes Catalyzed by N-Heterocyclic Carbenes. *Adv Synth Catal* 350(17):2715–2718. <https://doi.org/10.1002/adsc.200800532>
- Wang XN, Shao PL, Lv H, Ye S (2009) Enantioselective Synthesis of β -Trifluoromethyl- β -lactones via NHC-Catalyzed Ketene–Ketone Cycloaddition Reactions. *Org Lett* 11(18):4029–4031. <https://doi.org/10.1021/ol901290z>
- Wang XN, Shen LT, Ye S (2011) NHC-catalyzed enantioselective [2+ 2] and [2+ 2+ 2] cycloadditions of ketenes with isothiocyanates. *Org Lett* 13(24):6382–6385. <https://doi.org/10.1002/adsc.201000187>
- Douglas J, Taylor JE, Churchill G, Slawin AM, Smith AD (2013) NHC-Promoted asymmetric β -lactone formation from arylalkylketenes and electron-deficient benzaldehydes or pyridinecarboxaldehydes. *J Org Chem* 78(8):3925–3938. <https://doi.org/10.1021/jo4003079>
- Mondal M, Ibrahim AA, Wheeler KA, Kerrigan NJ (2010) Phosphine-catalyzed asymmetric synthesis of β -lactones from arylketenes and aromatic aldehydes. *Org Lett* 12(8):1664–1667. <https://doi.org/10.1021/ol100075m>
- Mukulesh M, Shi C, Nabil O (2015) Phosphine-Catalyzed Diastereoselective Synthesis of β -Lactones from Disubstituted Ketenes and α -Chiral Oxaldehydes. *J Org Chem* 80:5789–5794. <https://doi.org/10.1021/acs.joc.5b00869>
- Chidara S, Lin YM (2009) Reaction rate acceleration enabled by tethered Lewis acid-Lewis base bifunctional catalysis: A catalytic, enantioselective [2+ 2] ketene aldehyde cycloaddition reaction. *Synlett* 2009(10):1675–1679. <https://doi.org/10.1055/s-0029-1217332>
- Capurro P, Lambruschini C, Lova P, Moni L, Basso A (2021) Into the blue: ketene multicomponent reactions under visible light. *J Org Chem* 86(8):5845–5851. <https://doi.org/10.1021/acs.joc.1c00278>
- Basso A, Banfi L, Garbarino S, Riva R (2013) Ketene Three-Component Reaction: A Metal-Free Multicomponent Approach to Stereodefined Captodative Olefins. *Angew Chem Int Ed* 52(7):2096–2099. <https://doi.org/10.1002/anie.201209399>
- Garbarino S, Banfi L, Riva R, Basso A (2014) Three in the spotlight: photoinduced stereoselective synthesis of (Z)-acyloxyacrylamides through a multicomponent approach. *J Org Chem* 79(8):3615–3622. <https://doi.org/10.1021/jo500535f>
- Ibba F, Capurro P, Garbarino S, Anselmo M, Moni L, Basso A (2018) Photoinduced Multicomponent Synthesis of α -Silyloxy Acrylamides, an Unexplored Class of Silyl Enol Ethers. *Org Lett* 20(4):1098–1101. <https://doi.org/10.1021/acs.orglett.8b00009>
- Minuto F, Lambruschini C, Basso A (2021) Ketene 3-Component Staudinger Reaction (K-3CSR) to β -Lactams: A New Entry in the Class of Photoinduced Multicomponent Reactions. *Eur J Org Chem* 2021(22):3270–3273. <https://doi.org/10.1002/ejoc.202100577>
- Zuo WF, Liu Q, Xie X, Pang Q, Li W, Peng C, Li X, Han B (2023) Lighting the way to diverse cyclic architectures: expanding the horizons with photogenerated ketenes in sustainable chemistry. *Org Chem Front* 10(18):4474–4487. <https://doi.org/10.1039/D3QO00831B>
- D'Auria M (2019) The Paternò-Büchi reaction – a comprehensive review. *Photochem Photobiol Sci* 18:2297–2362. <https://doi.org/10.1039/C9PP00148D>
- Fréneau M, Hoffmann N (2017) The Paternò-Büchi reaction-Mechanisms and application to organic synthesis. *J Photochem Photobiol C: Photochem Rev* 33:83–108. <https://doi.org/10.1016/j.jphotochemrev.2017.10.002>
- Tinelli R, Ravelli D, Basso A, Tarantino SC, Capaldo L (2022) Catalyst-free [2+ 2] photocycloadditions between benzils and olefins under visible light. *Photochem Photobiol Sci* 21(5):695–703. <https://doi.org/10.1007/s43630-021-00129-4>
- Zhang QB, Yang Y, Zhang S, Liu Q (2023) Navigating Visible-Light-Triggered (aza and thia) Paternò-Büchi Reactions for the Synthesis of Heterocycles. *Adv Synth Catal*. <https://doi.org/10.1002/adsc.202300702>
- Franceschi P, Cuadros S, Goti G, Dell'Amico L (2023) Mechanisms and synthetic strategies in visible light-driven [2+2]-heterocycloadditions. *Angew Chem Int Ed* 62(8):e202217210. <https://doi.org/10.1002/anie.202217210>
- Baldwin JE, Roberts JD (1963) Structure and rearrangement of neutral phenylketene dimer. *J Am Chem Soc* 85(16):2444–2445. <https://doi.org/10.1021/ja00899a023>
- Ibrahim AA, Wei PH, Harzmann GD, Nalla D, Monda M, Wheeler KA, Kerrigan NJ (2021) Phosphine-catalyzed stereoselective dimerizations of ketenes. *Tetrahedron* 78:131838. <https://doi.org/10.1016/j.tet.2020.131838>
- Fu L, Wang H, Davies HM (2014) Role of ortho-substituents on rhodium-catalyzed asymmetric synthesis of β -lactones by intramolecular C-H insertions of aryl diazoacetates. *Org Lett* 16(11):3036–3039. <https://doi.org/10.1021/ol5011505>
- Imai T, Nishida S (1980) Thermolyses of 3-alkyl-4-phenyl-2-oxetanones and related compounds. *J Org Chem* 45(12):2354–2359
- Hussain ST, Ollis WD, Smith C, Stoddart JF (1975) The stereochemistry of 2, 4- and 2, 3-disubstituted- γ -butyrolactones. *J Chem Soc Perkin Trans 1*(15):1480–1492. <https://doi.org/10.1039/P19750001480>
- Workman J Jr (2002) The state of multivariate thinking for scientists in industry: 1980–2000. *Chemometr Intell Lab Syst* 60(1–2):13–23. [https://doi.org/10.1016/S0169-7439\(01\)00182-4](https://doi.org/10.1016/S0169-7439(01)00182-4)
- Nori V, Sinibaldi A, Pesciaioi F, Carlone A (2022) Impact of Design of Experiments in the Optimisation of Catalytic Reactions in Academia. *Synth* 54(19):4246–4256. <https://doi.org/10.1055/a-1736-6703>
- Mateos J, Rigodanza F, Costa P, Natali M, Vega-Peñalosa A, Fresch E, Collini E, Bonchio M, Sartorel A, Dell'Amico L (2022) Unveiling the impact of the light source and steric factors on [2 + 2] heterocycloaddition reactions. *Nat Synth* 2:26–36. <https://doi.org/10.1038/s44160-022-00191-5>
- Wegner J, Ceylan S, Kirschning A (2012) Flow chemistry—a key enabling technology for (multistep) organic synthesis. *Adv Synth Catal* 354(1):17–57. <https://doi.org/10.1002/adsc.201100584>
- Porter G, Suppan P (1964) Reactivity of excited states of aromatic ketones. *Pure Appl Chem* 9(4):499–506. <https://doi.org/10.1351/pac196409040499>
- Griesbeck AG, Bondock S (2008) Photocycloaddition of 5-Methoxyoxazolones to Aldehydes and α -Keto Esters: A Comprehensive View on Stereoselectivity, Triplet Biradical Conformations, and Synthetic Applications of Paternò-Büchi Adducts. *Aust J Chem* 61:573–580. <https://doi.org/10.1071/CH08168>
- Guerra C, Ayarde-Henríquez L, Duque-Noreña M, Chamorro E (2021) Unraveling the bonding nature along the photochemically activated Paternò-Büchi reaction mechanism. *Chem. Phys. Chem.* 22(22):2342–2351. <https://doi.org/10.1002/cphc.202100594>
- Morantz DJ, Wright AJC (1971) Structures of the excited states of benzil and related dicarbonyl molecules. *J Chem Phys* 54(2):692–697. <https://doi.org/10.1063/1.1674897>
- The stability of the wavefunction for this open-shell singlet diradical intermediate (^1Int) has been carefully checked via the “stable=opt” keyword implemented in G16
- Ravelli D, Protti S, Albini A (2015) Energy and molecules from photochemical/photocatalytic reactions. An overview *Mol* 20(1):1527–1542. <https://doi.org/10.3390/molecules20011527>
- Leardi R (2009) Experimental design in chemistry: A tutorial. *Anal Chim Acta* 652(1–2):161–172. <https://doi.org/10.1016/j.aca.2009.06.015>

41. Bracken C, Baumann M (2023) Synthesis of Highly Reactive Ketenimines via Photochemical Rearrangement of Isoxazoles. *Org Lett* 25(35):6593–6597. <https://doi.org/10.1021/acs.orglett.3c02556>
42. Garcia-Lacuna J, Baumann M (2023) Modular Photochemical Flow Synthesis of Structurally Diverse Benzyne and Triazine Precursors. *Adv Synth Catal* 365(15):2628–2635. <https://doi.org/10.1002/adsc.202300414>
43. Colella M, Gelato Y, Andresini M, Graziano E, Vilé G, Degenaro L, Luisi R (2023) Forging C–S Bonds on the Azetidine Ring by Continuous Flow Photochemical Addition of Thiols and Disulfides to Azetines. *Eur J Org Chem* 26(33):e202300413. <https://doi.org/10.1002/ejoc.202300413>
44. Griesbeck AG, Mauder H, Stadtmüller S (1994) Intersystem Crossing in Triplet 1,4-Biradicals: Conformational Memory Effects on the Stereoselectivity of Photocycloaddition Reactions. *Acc. Chem. Res* 27(3):70–75. <https://doi.org/10.1021/ar00039a002>
45. Griesbeck AG, Abe M, Bondock S (2004) Selectivity Control in Electron Spin Inversion Processes: Regio- and Stereochemistry of Paternò-Büchi Photocycloadditions as a Powerful Tool for Mapping Intersystem Crossing Processes. *Acc Chem Res* 37(12):919–928. <https://doi.org/10.1021/ar040081u>
46. Kutateladze AG (2001) Conformational Analysis of Singlet-Triplet State Mixing in Paternò-Büchi Diradicals. *J Am Chem Soc* 123(38):9279–9282. <https://doi.org/10.1021/ja016092p>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.