Organic Dye Photocatalyzed Synthesis of Functionalized Lactones and Lactams via a Cyclization-Alkynylation Cascade

Diana Cavalli,[a] and Jerome Waser*[a]

[a]   D. Cavalli, Prof. Dr. J. Waser
       Laboratory of Catalysis and Organic Synthesis
       Institute of Chemical Sciences and Engineering
       Ecole Polytechnique Fédérale de Lausanne
   1015 Lausanne
       E-mail: jerome.waser@epfl.ch

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Abstract: An organic dye photocatalyzed lactonization-alkynylation of easily accessible homoallylic cesium oxalates using ethynylbenziodoxolones (EBXs) reagents has been developed. The reaction gave access to valuable functionalized lactones and lactams in up to 88% yield via the formation of two new C-C bonds. The transformation was carried out on primary, secondary and tertiary homoallylic alcohols and primary homoallylic amines and could be applied to the synthesis of spirocyclic compounds, as well as fused and bridged bicyclic lactones.

γ-Lactones and -lactams are found in numerous agrochemicals, pharmaceuticals and bioactive natural products (Scheme 1A). For example, spironolactone (**1a**) is used to treat heart failure,[1] strigol (**1b**) inhibits plant-shoots branching[2] and nirmatrelvir (**1c**) is used for the treatment of COVID-19.[3] Hence, various synthetic approaches have been developed over the years to construct γ-lactones, mainly focusing on the formation of C−O bonds (Scheme 1B). Esterification of 1,4-hydroxy acids, Baeyer-Villiger oxidation and cyclization of carboxylic acids onto olefins are among the most frequently used methods.[4]

In contrast, the synthesis of γ-lactones and –lactams via C-C bond formation has been less investigated, although it has potential for a more convergent construction of the carbon backbone of the molecules. Radical-based approaches are especially attractive due to their high functional group tolerance, mild reaction conditions and lower sensibility towards steric hindrance. In particular, the 5-*exo*-trig cyclization of an alkoxycarbonyl radical onto an olefin is an attractive strategy as the radical precursor can be generated from easily accessible homoallylic alcohols and the radical generated after cyclization can be trapped by a SOMOphile, hence allowing multi-functionalization reactions (Scheme 1C).[5] In this regard, lactonization has been reported using selenocarbonates,[6] N-alkoxyoxalyloxy-2-thiopyridones[7] and S-alkoxycarbonyl xanthates[8] under classical conditions for the generation of radicals. The formed alkyl radicals were then trapped by a hydrogen atom, a thiopyridine or a xanthate moiety, with only one example of double C−C bond formation in a 5-*exo*-trig – *Giese* addition sequence.[7] More recently, Overman and coworkers reported the synthesis of arylated and vinylated spirolactones *via* a photoredox-catalyzed alkoxycarbonyl radical cyclization – Ni-catalyzed cross-coupling cascade using easily accessible homoallylic cesium oxalates as substrates and an iridium photocatalyst (Scheme 1D).[9]
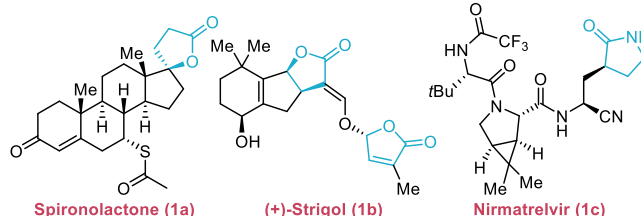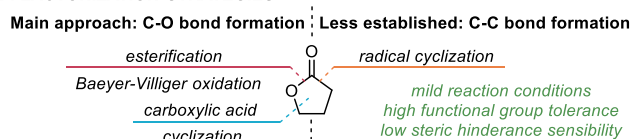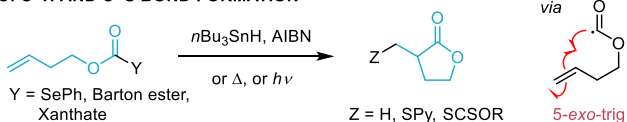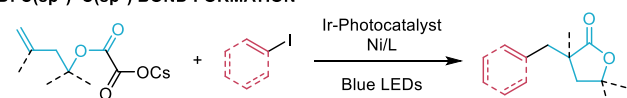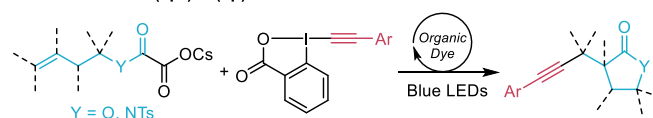

Scheme 1. γ−Lactones and γ−Lactams: importance in pharmaceutical and agrochemical industries (**A**) and synthetic strategies (**B-E**).

The reported examples allowed formation of a second C-C bond including a C(sp^3) or C(sp^2) carbon. However, there is no example of a C(sp^3)-C(sp) bond formation. Alkynes are versatile functional groups with applications in various fields such as medicinal chemistry, chemical biology and materials science.[10] Along the various radical approaches developed over the years to access alkynylated compounds, ethynylbenziodoxolones (EBXs) have been shown to be efficient radical traps.[11,12,13] Furthermore,

Leonori and coworkers have shown that EBXs can be used to terminate photoredox-catalyzed radical cyclization-alkynylation cascade reactions.[14]

In our previous work on the alkynylative deoxygenation of cesium oxalates, we had observed a single example of cyclization-alkynylation on a pre-organized rigid substrate.[15] Herein, we introduce a general method for the synthesis of γ-lactones and – lactams starting from easily-accessible homoallylic cesium oxalates using an organic dye and EBXs as radical traps through an efficient lactonization-alkynylation cascade (Scheme 1E).

Based on previous reports on photomediated alkynylation,[15,16] we started our investigation using homoallylic cesium oxalate **2a** as starting material, 1.5 equiv. of PhEBX (**3a**) as SOMOphile and 5 mol% 4CzIPN (**4a**) as photocatalyst (Table 1). After irradiation (44 W, 440 nm) in DCM overnight, the desired spirolactone **5a** was obtained in 53% yield (entry 1). Changing the photocatalyst for the more oxidizing 4ClCzIPN (**4b**)[17] provided **5a** in 64% yield (entry 2). The chlorinated solvent could be replaced by DMSO without change in yield (entry 3). In order to avoid polymerization of the starting material **2a**, lowering its concentration to 0.05 M and the catalyst loading to 2%, while keeping the concentration of PhEBX (**3a**) to 1.5 M provided spirolactone **5a** in 75% yield (entry 4). The yield could be further improved to 80% by lowering the power of the light source to 22 W and stirring the reaction for 42 h (entry 5). Finally, when the reaction was performed in absence of any photocatalyst, **5a** was obtained in 14% yield due to the innate photoactivity of PhEBX (**3a**)[15] (entry 6). In absence of light no product was observed (entry 7).

With the optimized conditions in hand, we first investigated the scope of the lactonization reaction on tertiary alcohols to obtain valuable spirolactones (Scheme 2A). The model substrate **2a** cyclized smoothly on 0.3 mmol scale, giving **5a** in 76% isolated yield. Furthermore, performing the same reaction on 3.0 mmol scale provided **5a** in 69% yield. Spiroheterocycles **5b** and **5c** were obtained in 86% and 70% yield, respectively. The size of the second ring in the spirocycle could be varied broadly to give compounds **5d**, **5e** and **5f** in 77%, 81% and 74% yield, respectively. The dehydroepiandrosterone-derived spirolactone **5g** was obtained in 50% yield and 3:1 dr.

Having established the scope of tertiary alcohols, we moved our attention to secondary homoallylic cesium oxalates (Scheme 2B). This class of substrates had not been investigated by Overman and co-workers.[9] Lactone **5h** having a pendent alkyl chain could be isolated in 55% yield and 3:2 dr. Furthermore, performing the reaction from *trans*-1,2-vinyl-cyclohexanol provided the *trans* 6/5 fused lactone **5i** in 56% yield and perfect diastereoselectivity. Additionally, the bridged compound **5j** was isolated in 25% yield as a single diastereoisomer.

Finally, the alkynyl-lactonization reaction was performed on primary homoallylic cesium oxalates (Scheme 2C). We used this class of substrates to study the difference in reactivity of the primary, secondary or tertiary radical intermediate formed after cyclization in the alkynylation step. In the case of C(sp^3)-C(sp^2) bond formation, only primary intermediates had been reported.[9] Lactone **5k** resulting from alkynylation of a primary radical intermediate was obtained in 62% yield, while a *cis*-hexenol-derived cesium oxalate cyclized in 70% yield and 4:3 dr through
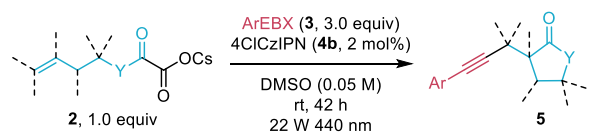
the alkynylation of a secondary radical to give **5l**. Lactone **5m**, which arose from a tertiary radical intermediate, was isolated in 40% yield. We speculate that the trapping of the radical with PhEBX (**3a**) was less efficient in this case due to steric congestion.

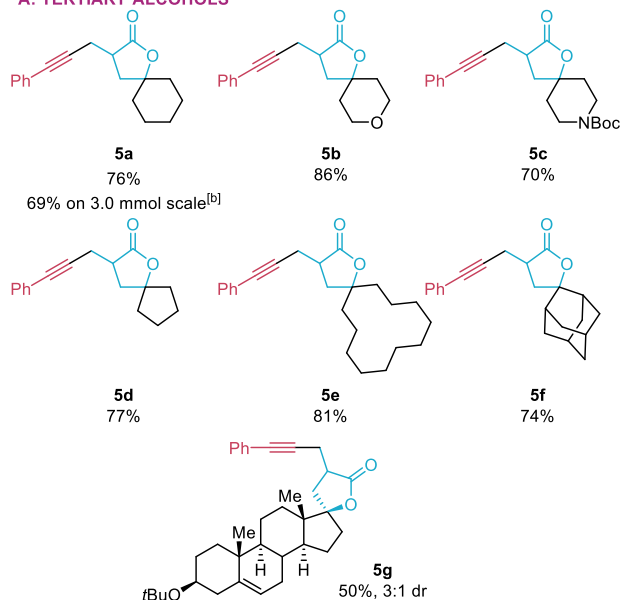**Table 1.** Optimization of the reaction conditions.[a]

Entry	Modification from standard conditions	Yield (%) [b]
1	None	53
2	PC: 4ClCzIPN (**4b**)	64
3	As above, solvent: DMSO	62
4	3.0 equiv PhEBX (**3a**) PC: 4ClCzIPN (**4b** 2 mol%) Solvent: DMSO (0.05 M)	75
5	As above, 22 W light source, 42 h	80
6	As above, no PC	14
7	no light source	0

[a] Reaction conditions: 0.1 mmol **2a**, 1.5 equiv PhEBX (**3a**), 0.5 mol% 4CzIPN (**4a**), DCM (0.1 M), 44 W 440 nm LEDs, rt, 18 h. [b] Yields determined by ^{1}H NMR spectroscopy using mesitylene as internal standard.
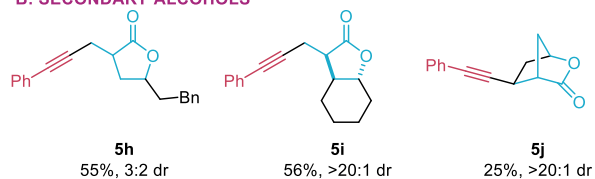
In addition to lactones, we were interested to apply the same reaction conditions on homoallylic cesium oxamates to obtain alkynylated γ-lactams. To our delight, a simple primary tosyl-protected amide provided lactam **5k** in 71% yield. The structure of **5k** was confirmed by X-Ray crystallography.[18] Also, a *cis*-hexenamine derivative cyclized successfully to give **5o** in 63% yield and 2:1 dr. Despite several attempts, tertiary homoallylic cesium oxamates only provided the product resulting from alkynylation of the aminocarbonyl radical prior to cyclization. We speculate that the 5-*exo*-trig cyclization is not occurring due to a non-favorable conformation of the aminocarbonyl radical.[19] Nevertheless, spirolactam **5p** with a different connectivity can still
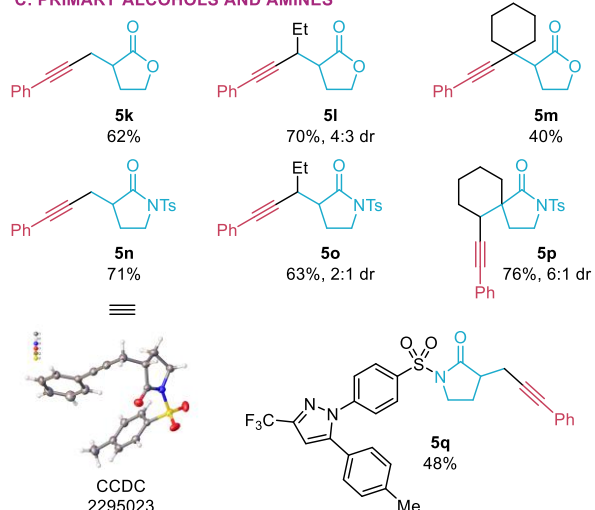
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A: TERTIARY ALCOHOLS

5a
76%
69% on 3.0 mmol scale[b]

5b
86%

5c
70%

5d
77%

5e
81%

5f
74%

5g
50%, 3:1 dr

B: SECONDARY ALCOHOLS

5h
55%, 3:2 dr

5i
56%, >20:1 dr

5j
25%, >20:1 dr

C: PRIMARY ALCOHOLS AND AMINES

5k
62%

5l
70%, 4:3 dr

5m
40%

5n
71%

5o
63%, 2:1 dr

5p
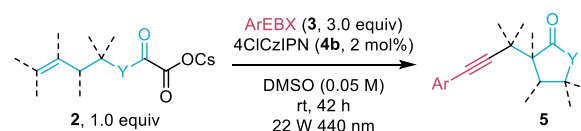76%, 6:1 dr

CCDC 2295023

5q
48%

Scheme 2. Oxalate and oxamate scope of the reaction.[a] [a] Reaction conditions: 0.3 mmol cesium oxalate or oxamate (**2**), 3.0 equiv ArEBX (**3**), 2 mol% 4ClCzIPN (**4b**), DMSO (0.05 M), 22 W 440 nm LEDs, rt, 42 h. [b] Modifications: 44 W LEDs, 18 h.
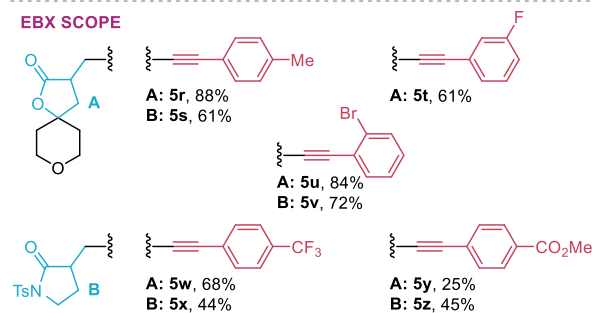
the lactamization-alkynylation reaction was performed using a Celecoxib derivative to afford lactam **5q** in 48% yield, demonstrating that more complex functionalized sulfonimides were tolerated in the reaction.

The scope of the Ar-EBX reagents was then explored on both lactonization and lactamization reactions, using either cesium oxalate **2a** or cesium oxamate **2n** (Scheme 3). *p*TolEBX (**3b**) provided compounds **5r** and **5s** in 88% and 61% yield, respectively. Halogenated Ar-EBX reagents **3c** and **3d** were tolerated under the reaction conditions: the fluorinated compound **5t**, was isolated in 61% yield; while brominated EBX reagent **3d** provided cyclized products **5u** and **5v** in 84% and 72% yield, respectively. Finally, aryl alkynes containing electron-withdrawing groups such as trifluoromethyl (**5w** and **5x**) and methyl ester (**5y** and **5z**) were obtained in 68%, 44%, 25% and 45% yield, respectively.
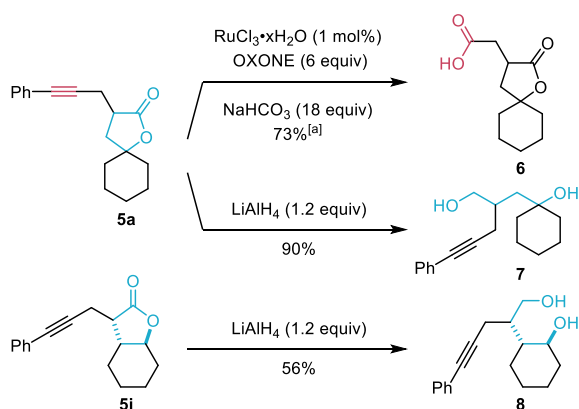

EBX SCOPE

A: **5r**, 88%
B: **5s**, 61%

A: **5t**, 61%

A: **5u**, 84%
B: **5v**, 72%

A: **5w**, 68%
B: **5x**, 44%

A: **5y**, 25%
B: **5z**, 45%

Scheme 3. Alkyne scope of the reaction.[a] [a] Reaction conditions: 0.3 mmol cesium oxalate or oxamate (**2**), 3.0 equiv ArEBX (**3**), 2 mol% 4ClCzIPN (**4b**), DMSO (0.05 M), 22 W 440 nm LEDs, rt, 42 h.

In order to demonstrate the synthetic utility of the obtained alkynylated spirolactones, post functionalization reactions were carried out from **5a** (Scheme 4). First, we envisaged to introduce a different synthetic handle than the alkyne. Therefore, spirolactone **5a** was subjected to a *one-pot* Ru-catalyzed 1,2-diketone formation – Baeyer Villiger oxidation procedure, giving carboxylic acid derivative **6** in 73% yield.[20] Second, the lactone was opened reductively by treatment with LiAlH$_4$ leading to 1,4-diol **7** having a pendent alkynyl group in 90% yield. Finally, the same reaction conditions were applied to lactone **5i**, which had been obtained as a single diastereoisomer, to provide diol **8** in 56% yield. This sequence therefore allowed to install three contiguous stereocenters with high relative stereocontrol.

be obtained in 76% yield and 6:1 dr starting from a cyclohexenylethylamine oxamate as radical precursor. Finally,

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Scheme 4. Product modifications. [a] Yield determined by ^{1}H NMR spectroscopy using mesitylene as internal standard.

Scheme 5 details a speculative mechanism, for the lactonization-alkynylation reaction of homoallylic oxalates **2** based on literature precedence,[15,21,22,23]. Light irradiation would result in the excitation of 4ClCzIPN (**4b**, PC) to its excited state 4ClCzIPN* (PC*). PC* ($E_{1/2}$(PC*/PC•⁻) = +1.71 V vs SCE in MeCN)[15] would then undergo single electron transfer (SET) from oxalate salt **2a** ($E_{1/2}$(**2a**⁻/**2a**•) = +1.28 V vs SCE in MeCN for *t*BuOCOCO₂Cs)[21] generating radical **I**. Intermediate **I** would then undergo fast decarboxylation, generating the alkoxycarbonyl radical **II**. This intermediate, instead of losing a second equivalent of CO₂, would undergo 5-*exo*-trig cyclization with the alkene forming radical intermediate **III**.[22] The latter is then trapped by PhEBX (**3a**) generating the desired alkynyl-γ-lactone **5a** and iodanyl radical **IV** ($E_{1/2}$(**IV**•/**IV**⁻) ≈ −0.25 V),[23] which would then turn over the photocatalyst $E_{1/2}$(PC/PC•⁻) = −0.97 V vs SCE in MeCN) and generate iodobenzoate (**9**).
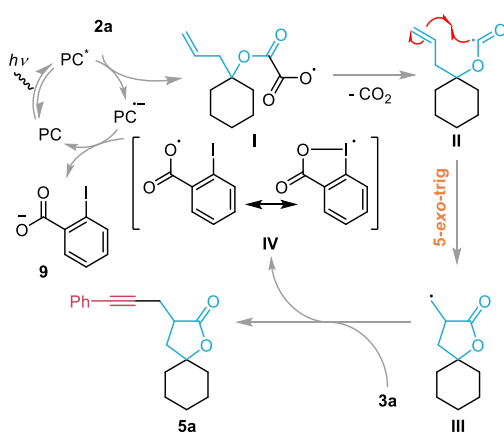
Scheme 5. Proposed mechanism for the lactonization-alkynylation.

In conclusion, a metal-free photocatalyzed lactonization-alkynylation reaction of homoallylic cesium oxalates has been developed. In addition to valuable spirolactones, bicyclic compounds and substituted lactones and lactams were also

obtained. Moreover, various halogenated- and electron-donating or –withdrawing groups containing EBX reagents were successfully used in the reaction. Finally, the synthetic utility of the obtained compounds was demonstrated by transforming the alkyne into a carboxylic acid and reducing the lactones to 1,4-diols.

Supporting Information

The authors have cited additional references within the Supporting Information.[24-36] General methods, experimental procedures and analytical data for all new compounds. ^{1}H NMR and ^{13}C NMR spectra.

Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

[1]   A. Quintavalla, *Curr. Med. Chem.* **2018**, *25*, 917 – 962.

[2]   S. K. Sartori, M. A. N. Diaz, G. Diaz-Muñoz, *Tetrahedron* **2021**, *84*, 132001.

[3]   D. R. Owen, C. M. N Allerton, A. S. Anderson, L. Aschenbrenner, M. Avery, S. Berritt, B. Boras, R. D. Cardin, A. Carlo, K. J. Coffman, A. Dantonio, L. Di, H. Eng, R. Ferre, K. S. Gajiwala, S. A. Gibson, S. E. Greasley, B. L. Hurst, E. P. Kadar, A. S. Kalgutkar, J. C. Lee, J. Lee, W. Liu, S. W. Mason, S. Noell, J. J. Novak, R. Scott Obach, K. Ogilvie, N. C. Patel, M. Pettersson, D. K. Rai, M. R. Reese, M. F. Sammons, J. G. Sathish, R. P. Shankar Singh, C. M. Steppan, A. E. Stewart, J. B. Tuttle, L. Updyke, P. R. Verhoest, L. Wei, Q. Yang, Y. Zhu, *Science* **2021**, *374*, 1586–1593.

[4]   B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Chem. Rev.* **2017**, *117*, 10502 – 10566.

[5]   a) M. Albert, L. Fensterbank, E. Lacôte, M. Malacria, *Top. Curr. Chem.* **2006**, *264*, 1 – 62. b) Y. Zhao, Y. Lv, W. Xia, *Chem. Rec.* **2019**, *19*, 424 – 439.

[6]   a) M. D. Bachi, E. Bosch, *Tetrahedron Lett.* **1988**, *29*, 2581 – 2584; b) M. D. Bachi, E. Bosch, *J. Org. Chem.* **1992**, *57*, 4696 – 4705.

4

[7]   a) H. Togo, M. Yokoyama, *Heterocycles* **1990**, *31*, 437 – 441; b) H. Togo, M. Fujii, M. Yokoyama, *Bull. Chem. Soc. Jpn* **1991**, *64*, 57 – 67.

[8]   J. E. Forbes, R. N. Saicic, S. Z. Zard, *Tetrahedron*, **1999**, *55*, 3791 – 3802.

[9]   N. A. Weires, Y. Slutskyy, L. E. Overman, *Angew. Chem. Int. Ed.* **2019**, *58*, 8561 – 8565.

[10]   a) T. T. Talele, *J. Med. Chem.* **2020**, *63*, 5625 – 5663; b) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905 – 4979.

[11]   Seminal work on radical-based alkynylation using EBXs: X. Liu, Z. Wang, X. Cheng, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 14330 – 14333.

[12]   For a comprehensive review on radical-based alkynylation reactions see: F. Le Vaillant, J. Waser, *Chem. Sci.* **2019**, *10*, 8909 – 8923.

[13]   For a recent review on the use of EBXs in alkynylation reactions see: E. Le Du, J. Waser, *Chem. Commun.* **2023**, *59*, 1589 – 1604.

[14]   J. Davies, N. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* **2017**, *56*, 13361 – 13365.

[15]   S. G. E. Amos, D. Cavalli, F. Le Vaillant, J. Waser, *Angew. Chem. Int. Ed.* **2021**, *60*, 23827 – 23834.

[16]   For a review on cyanoarenes as photocatalysts see: A. Tlili, S. Lakhdar, *Angew. Chem. Int. Ed.* **2021**, *60*, 19526 – 19549.

[17]   F. Le Vaillant, M. Garreau, S. Nicolai, G. Gryn'Ova, C. Corminboeuf, J. Waser, *Chem. Sci.* **2018**, *9*, 5883 – 5889.

[18]   Deposition Number 2295023 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[19]   See the Supporting Information for more details.

[20]   D. Yang, F. Cheng, Z. – M. Dong, D. – W. Zhang, *J. Org. Chem.* **2004**, *69*, 2221 – 2223.

[21]   C. C. Nawrat, C. R. Jamison, Y. Slutskyy, D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.

[22]   The rate constant for the second decarboxylation and for the 5-*exo* cyclization were elucidated by laser flash photolysis kinedic studies: P. A. Simakov, F. N. Martinez, J. H. Horner, M. Newcomb, *J. Org. Chem.* **1998**, *63*, 1226 – 1232.

[23]   The value for the oxidation of the iodanyl radical was computed: F. Le Vaillant, M. Wodrich, J. Waser, *Chem. Sci.* **2017**, *8*, 1790 – 1800.

[24]   B. Liu, C.-H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2018**, *140*, 12829 – 12835.

[25]   R. W. Freerksen, W. E. Pabst, M. L. Raggio, S. A. Sherman, R. R. Wroble, D. S. Watt, *J. Am. Chem. Soc.* **1977**, *99*, 1536 – 1542.

[26]   T. Wang, X.-Q. Hao, J.-J. Huang, J.-L. Niu, J.-F. Gong, M.-P. Song, *J. Org. Chem.* **2013**, *78*, 8712 – 8721.

[27]   D. Tobia, B. Rickborn, *J. Org. Chem.* **1989**, *54*, 777 – 782.

[28]   Launey, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, doi:10.3762/bjoc.6.41.

[29]   M. Schelwies, R. Paciello, R. Pelzer, W. Siegel, M. Breuer, *Chem. Eur. J.* **2021**, *27*, 9263 – 9266.

[30]   A. Fanourakis, N. J. Hodson, A. R. Lit, R. Phipps, *J. Am. Chem. Soc.* **2023**, *145*, 7516 – 7527.

[31]   E. L. Lucas, K. A. Hewitt, P.-P. Chen, A. J. Castro, X. Hong, E. R. Jarvo, *J. Org. Chem.* **2020**, *85*, 1775 – 1793.

[32]   J.-W. Wang, D.-G. Liu, Z. Chang, Z. Li, Y. Fu, X. Lu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205537.

[33]   G. Asensio, R. Mello, C. Boix-Bernardini, M. E. González-Núñez, G. Castellano, *J. Org. Chem.* **1995**, *60*, 3692 – 3699.

[34]   A. D. Jones, D. W. Knight, D. E. Hibbs, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 1182 – 1203.

[35]   T. M. Nguyen, D. A. Nicewicz, *J. Am. Chem. Soc.* **2013**, *135*, 9588 – 9591.

[36]   J. Y. Su, D. C. Grünenfelder, K. Takeuchi, S. E. Reisman, *Org. Lett.* **2018**, *20*, 4912 – 4916.

Entry for the Table of Contents

easily accessible from homoallylic alcohols and amines

valuable functionalized lactones and lactams
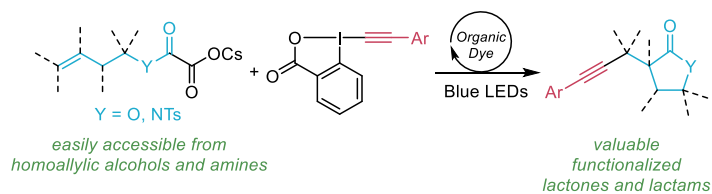
Valuable functionalized γ-lactones and γ-lactams can be obtained from easily accessible homoallylic cesium oxalates and oxamates *via* an organic dye photocatalyzed cyclization-alkynylation cascade terminated by ethynylbenziodoxolones (EBXs).

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