# Stereoselective visible light catalytic cyclization of bis(enones): a viable approach to the synthesis of enantiomerically enriched cyclopentane rings.

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Dedicated to Prof. Franco Cozzi on the occasion of his 70th birthday

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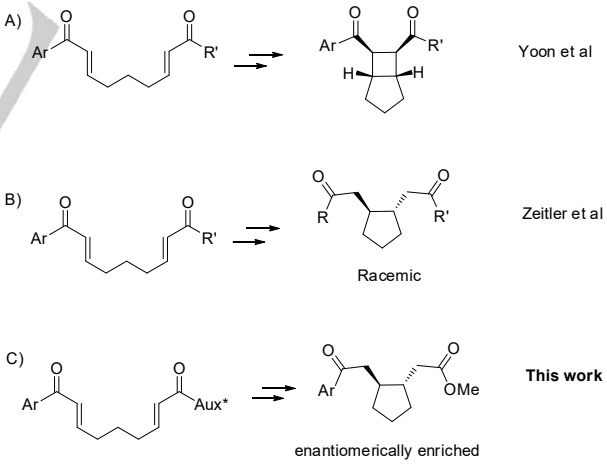
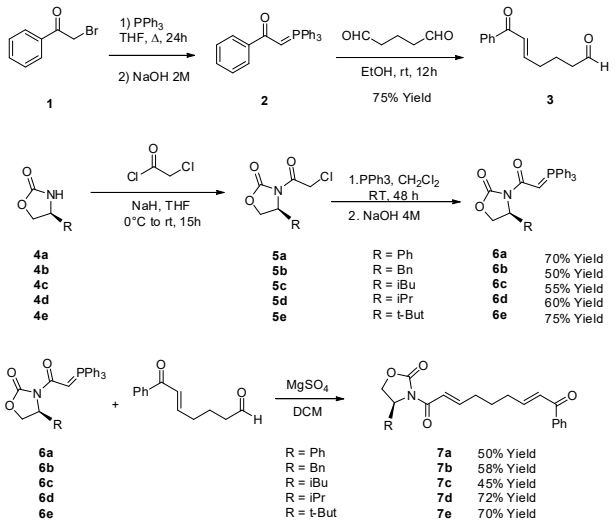
**Abstract:** Photoredox catalytic cyclization of aryl enones in the presence of visible light, promoted either by metals or organic dyes, represent a valuable strategy for the synthesis of cycloalkanes. The development of a stereoselective version of such transformation, in the presence of the metal-free catalyst Eosin Y was studied, with the aim to realize an efficient protocol for the in-flow synthesis of enantiomerically enriched functionalized cyclopentane rings, taking advantage of the flow reactors technology.
The use of a chiral auxiliary on the bisenone to be cyclized offers a straightforward and convenient option to exert a stereocontrol on the light-driven cyclization. By exploiting Evans' oxazolidinones, the stereoselective light-driven cyclization affords, after the removal of the chiral auxiliary, a functionalized 1,2-*trans* cyclopentane ring in up to 83/17 enantiomeric ratio. When the reaction was performed in continuo, in a homemade coil photoreactor, high yields were observed. The cyclization was also successfully realized in a 3D-printed mesoreactor, without any change in the diastereoseletctivity of the process.

Light represents an abundant, renewable, low cost and environmentally friendly resource resource to build new C-C bonds, exploring non-conventional synthetic pathways characterized by the presence of radical intermediates.[1] One of the most popular strategies to realize efficient reactions promoted by visible light involves the use of photosensitizers and photocatalysts, which, upon irradiation, serve as electron donors or electron acceptors.[2]
Many kinds of photocatalysts are known and are typically metal-based, such as iridium or ruthenium catalysts.[3] Based on the pioneering studies of Krische,[4] Yoon published in 2008 the Ru-based photoredox catalytic cyclization of bis-aryl enones in the presence of visible light (Scheme 1, A).[5] Soon after, Zeitler reported that also a commercially available and low cost organic dye, like Eosin Y, could be employed in the cyclization, to afford 1,2-substituted cyclopentane rings.[6] The combination of an organocatalytic thiourea with Eosin Y allowed to obtain in good yields racemic *trans*-1,2-cycloalkanes (Scheme 1, B).
We have decided to develop a stereoselective version of such transformation, and to realize an efficient protocol for the in-flow synthesis of enantiomerically enriched functionalized cyclopentane rings, taking advantage of the flow reactors technology,[7] including 3D-printed devices.[8]
The use of chiral catalysts is the most attractive option, [3d-e] but the setup of a successful chiral photocatalytic system is a very challenging task. We thought that the use of a chiral auxiliary on the bisenone to be cyclized could offer a straightforward and convenient option to exert a stereocontrol on the light-driven cyclization. The removal of the auxiliary, that can ben conveniently recovered, would afford enantiomerically enriched cyclopentanes (Scheme 1, C).




***Scheme 1.*** A stereoselective approach for the synthesis of enantiomerically enriched 1,2-*trans* cyclopentane rings.

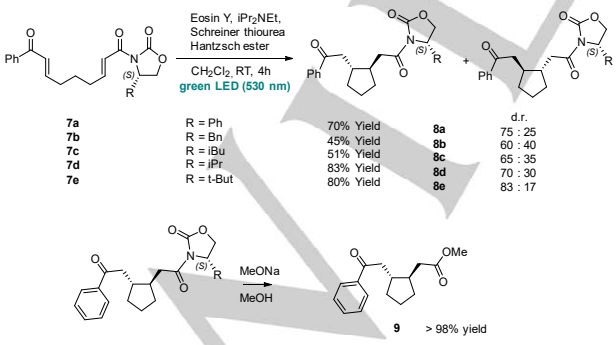
Our study started with the preparation of phenyl bis-enones featuring different chiral oxazolidinones, to verify the chemical compatibility of the chiral auxiliary with the photoredox conditions, and to investigate the ability of the different chiral units to control the stereochemical outcome of the cyclization (Scheme 2).




***Scheme* 2.** Synthesis of phenyl enones **7a-e** featuring different chiral oxazolidinones.

Starting from α-bromoacetophenone, ylide **2** was prepared and reacted with glutaric aldehyde to afford in 75% yield compound **3**, the common intermediate for the synthesis of different bisenones featuring a chiral moiety. Oxazolidinones **4a-e** were converted in 50-75% yields to the corresponding ylides **6a-e,** which were reacted with **3** to yield the enantiopure bisenones **7a-e** in 45-72% isolated yields, as *E,E* isomer as largely major diastereoisomer.[9]

Based on the experimental conditions reported in the previous works,[6] the in batch cyclization of derivatives **7a-e** was then studied in the presence of light (green LED at 530 nm) and Eosin Y (Scheme 3). In a 10 ml Schlenk tube equimolar amounts of the bisenone, $iPr_2NEt$ and Hantzsch ester, in the presence of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (0.2 eq) and 2.5% of Eosin Y in $CH_2Cl_2$ were irradiated for 4 h using green LEDs (see the Supporting Information for details on the LEDs characterization).

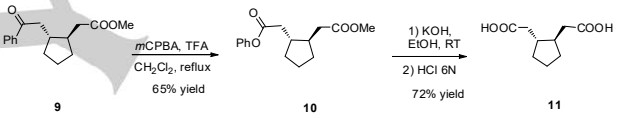



***Scheme* 3.** Synthesis of enantiomerically enriched cyclopentane **9** by cyclization of phenyl enones **7a-e** to afford cyclopentanes **8a-e**, followed by removal of the oxazolidinones ring.

Under the present conditions, the cyclization of compound **7a**, featuring the (S)-4-phenyloaxazolidinone ring, produced cyclopentane **8a** in 70% yield, >98/2 *trans/cis* selectivity and 75:25 diastereoisomeric ratio. The use of other chiral oxazolidinones in compounds **7b-d** did not lead to any improved diastereoselectivity, while the reaction of bisenone **7e**, featuring the (S)-4-*t*-butyloxazolidinone, led to the formation of cyclopentane **8e** in 80% yield, as single *trans* isomer and a 83/17 diastereoselectivity.[10] At the present, only a highly speculative mechanism and stereoselectivity model may be proposed, as working hypothesis; although the steric hindrance of the substituent on the oxazolidinone ring is responsible for the observed selectivity, since many different orientations in the space are possible for the chiral auxiliary moiety, further studies will be necessary to "lock" the auxiliary in a well defined confomation (see the supporting information for a proposed mechanism and a tentative stereoselection model).

The removal of the chiral auxiliary was realized by reaction with sodium methoxide in methanol,[11] to give in quantitative yield the enantiomerically enriched cyclopentane **9.** The enantiomeric excess was evaluated by HPLC analysis on chiral stationary phase and confirmed the diastereoisomeric ratio evaluated by NMR on purified products **8a-e.**

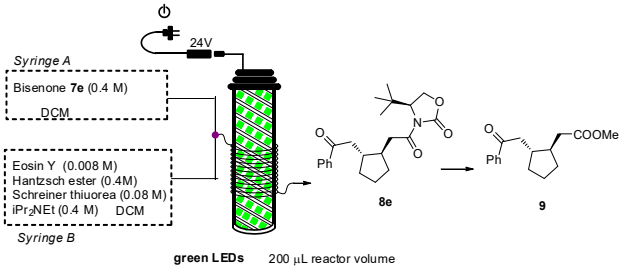
The absolute configuration of the major enantiomer of cyclopentane **9** was established by chemical correlation (Scheme 4).




***Scheme* 4.** Determination of absolute configuration of cyclopentane **9** obtained by stereoselective photocyclization.

Bayer-Villiger oxidation[12] of **9** led to the diester derivative **10**, that was hydrolysed to 2,2'-(-cyclopentane-1,2-diyl)diacetic acid **11**, whose absolute configuration was established to be (*1R, 2R*) by comparison of the optical rotatory power of the sample with the data reported in literature.I[13]

We then moved to study the diatereoselective cylicaztion under continuous flow condtions (Scheme 5).




***Scheme* 5.** In flow cyclization of aryl bisenones in a homemade coil photoredox reactor.

The advantages and the beneficial effects of performing a light-driven transformation in flow, and the possibility to overcome the well known limitations of the in batch reactions are well documented.[14] Therefore, we decided to perform the cyclization of bisenone **7e** in a homemade coil photoredox reactor (Scheme 5, see the Supporting Information for details on the device).

In a typical experiment, syringe A was filled with a 0.4 M solution of bisenone **7e** in DCM (total volume 500 μl). Syringe B was filled with a mixture obtained dissolving 2,6 mg (0,004 mmol) of Eosin Y, 50 mg (0.2 mmol) of Hantzsch ester, 20 mg (0.04 mmol) of Schreiner thiourea and 34 μl (0.2 mmol) of $iPrNEt_2$ in DCM (total volume 500 μl). Syringes A and B were connected to a syringe pump and the reagents were fed into PFA reactor through a T-junction at the desired flow rate (6.66 μL/min for 30 min residence time and 5 μL/min for 40 min residence time) at room temperature. Light irradiation was performed using Green LEDs. A dark shield was used as eye protection system. One reactor volume was discarded before starting sample collection in order to achieve steady-state conditions. Reaction outcome was collected in the dark into a vial and the crude was purified by column chromatography. We were pleased to find that under continuous flow conditions the product **8e** was obtained with the same diastereoselectivity as the batch reaction, as demonstrated by conversion of **8e** to ester **9** and determination of e.e. by HPLC analysis. With a 30 minutes residence time, 65% conversion was observed and **8e** was produced in 45% isolated yield; however, operating with a residence time of 40 minutes, a 90% conversion and 87% isolated yields were observed.

In figure 1 the setup configuration is reported.

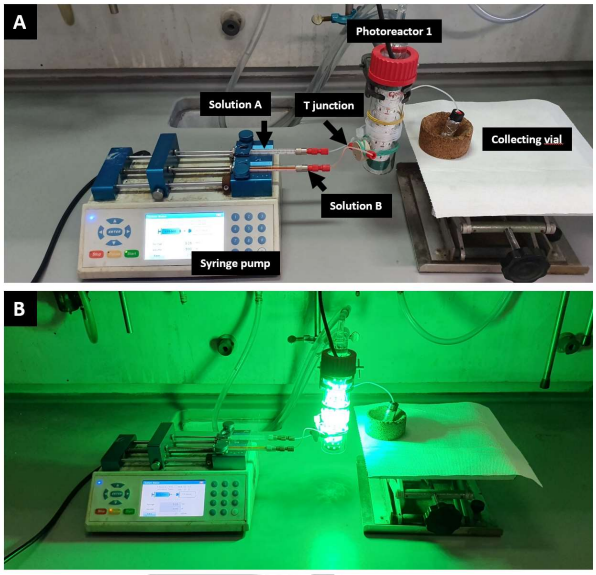



**Figure 1.** Reaction setup using homemade coil photoreactor. A) Device with green LEDs off, B) Device with green LEDs on.

We performed a preliminary investigation into the use of 3D-printed reactors (for the details on 3D-printed reactor fabrication see the Supporting Information).[15] The 500 μL reactor was realized using a Formlabs Form 2 3D printer (SLA Technology) with Clear v4 resin. The channels present a 1x1 $mm^2$ squared section.

The set up is reported in Figure 2.

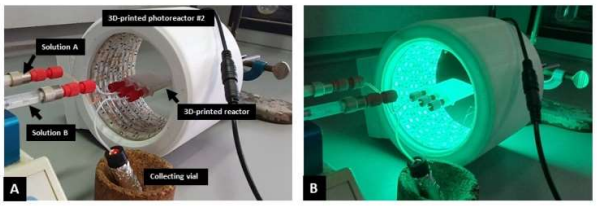



**Figure 2.** Reaction setup using 3D printed photoreactor. A) green LEDs off, B) green LEDs on.

The flow reactor was fed by a continuous flow of reagents and reactants: Syringes A and B, filled as described for the reaction in Scheme , were connected to a syringe pump and the reagents were fed into the 3D printed device at the desired flow rate at room temperature. Light irradiation was performed using Green LEDs. By operating with a 30 minutes residence time, the product was isolated in 50% yield and 78:22 level of stereoselectivity.

In conclusion, the use of the chiral auxiliary strategy to control the stereochemical outcome of the photoredox catalytic cyclization of bisenones has been studied. By employing Evans' oxazolidinones, the light driven cyclization afforded, after the auxiliary removal, a functionalized, enantiomerically enriched cyclopentane ring, in up to 83/17 enantioselectivity. Noteworthy, the reaction has been successfully performed under continuous flow conditions, both in a homemade photoredox coil reactor and in a 3D-printed mesoreactor, with good to excellent yields and no appreciable loss of stereoselectivity.

Although the level of stereocontrol cannot be considered satisfactory, and further studies are needed to improve the stereoselectivity of the process, the present study demonstrates the chiral auxiliary approach may indeed represent a valuable, and easy to explore, alternative option to realize diastereoselective, photoredox catalytic in-flow transformations.

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**Keywords:** photoredox • flow reactors • stereoselectivity • chiral auxiliary• visible light-driven reactions

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[9] The Wittig reaction produces the E,E isomer as largely major isomer (>80% diastereoselectivity), with only minor amounts of the E,Z isomer that, in some cases, could be isolated by chromatographic purification.

[10] The reaction was typically performed on the pure E,E isomer of the compounds **7a-e;** however, with products **7d** and **7e,** the cyclization was performed also on a mixture of isomers (E,E and E,Z) and gave the expected cyclopentane with no appreaciable difference in yield and diastereoselectivity.

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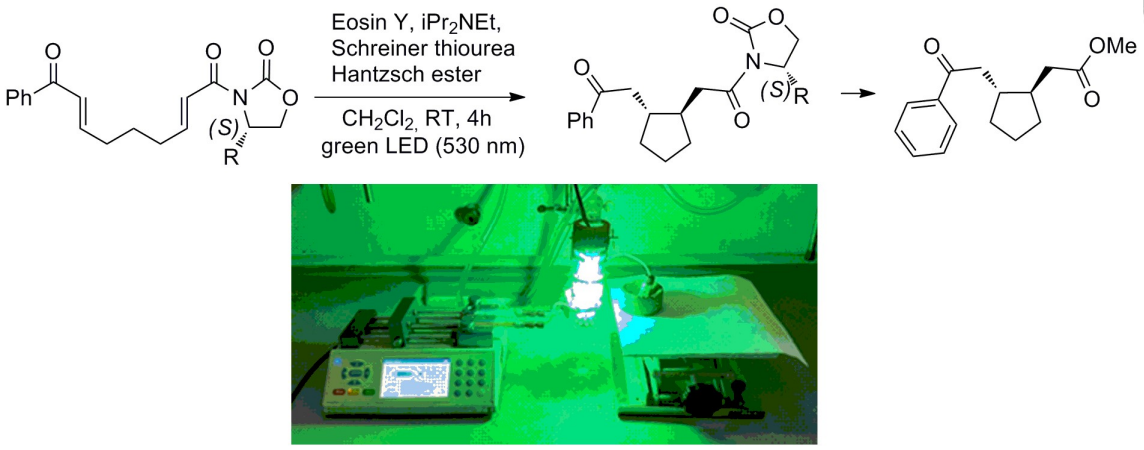


An efficient protocol for the in-flow synthesis of enantiomerically enriched functionalized cyclopentane rings has been developed. By exploiting Evans' oxazolidinones, the stereoselective light-driven cyclization of bisenones in a coil photoreactor affords, after the removal of the chiral auxiliary, an enantiomerically enriched cyclopentane. The cyclization was also successfully realized in a 3D-printed mesoreactor.