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# Asymmetric [2+2] photocycloaddition *via* charge transfer complex for the synthesis of tricyclic chiral ethers†

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**The asymmetric synthesis of chiral polycyclic ethers by an intramolecular [2+2] photocycloaddition is described. This process proceeded through a photocatalytically active iminium ion-based charge transfer (CT) complex under visible light irradiation. In this way a stereocontrolled [2+2] photocycloaddition is enabled leading to tricyclic products with good enantiomeric ratios.**

Chiral polycyclic compounds have a huge importance in medical chemistry since many bioactive molecules and drugs contain polycyclic scaffolds in their structures.[1] Among them, polycyclic ethers are found in many natural products (Fig. 1),[2] and some of the most useful and employed drugs in pain treatment, such as Morphine and Codeine, contain a 5-membered ring ether motif.[3] On the other hand, the corresponding 6-membered ring is found in the main core of rotenoids such as Rotenone, which is a naturally occurring insecticide and pesticide with anticancer properties, or in Anthopogochromane, a complex cyclobutane-containing natural product.[4,5] In addition, a polycyclic 7-membered ether scaffold is found in Enokipodin A, a compound isolated from nature which shows antimicrobial activity.[6]

On the other hand, the 4-membered ring motif of cyclobutanes is found in many natural products,[7] whereas cyclobutane derivatives have been employed as suitable building blocks and intermediates in organic synthesis and in the construction of biologically active molecules.[8,9] Considering the importance of this type of scaffold, new catalytic asymmetric synthetic routes should be explored to allow the obtainment of cyclobutanes in an enantioenriched form.

Photocatalysis has appeared as a new synthetic tool for the construction of organic molecules.[10] In this context, enantioselective intramolecular [2+2] photocycloaddition represents a straightforward strategy for the synthesis of chiral polycyclic molecules in a single step. The group of Bach described different asymmetric intramolecular [2+2] photocycloadditions employing hydrogen bonding or Lewis acid catalysis to induce stereocontrol.[11,12] In the first pioneering example, the use of a bifunctional xanthone-containing catalyst allowed the obtainment of the targeted cyclobutane *via* a triplet energy transfer mechanism (Scheme 1a).[11a] A second strategy reported by the same group unlocked the construction of interesting tricyclic compounds through the preferential photoexcitation of a chiral Lewis acid-substrate complex chromophore (Scheme 1b).[12a] In addition, other innovative photocatalytic strategies have been described by Yoon's and Meggers' research groups through different activation modes.[13] In this context, our research group has recently demonstrated that iminium ion catalysis and charge transfer (CT) complex photoactivity could be exploited for the synthesis of enantioenriched cyclobutanes *via* [2+2] photocycloaddition.[14] This strategy constituted an unprecedented aminocatalytic activation mode in [2+2] photocycloaddition, showcasing that the photoactivity of CT complexes is not limited to photoredox reactions but it can be exploited to unlock novel light-driven reactions.[15] With these precedents in mind, we investigated the intramolecular [2+2]

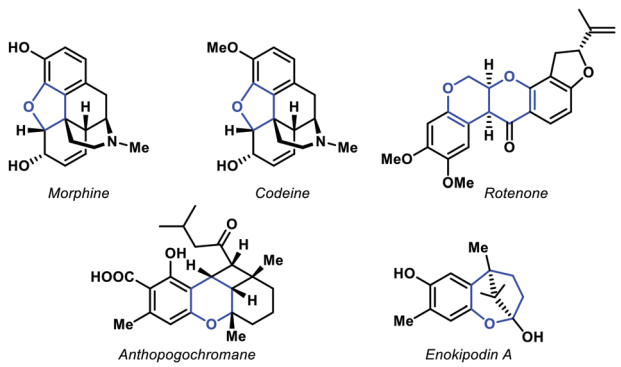


Fig. 1 Examples of biologically relevant polycyclic ethers.

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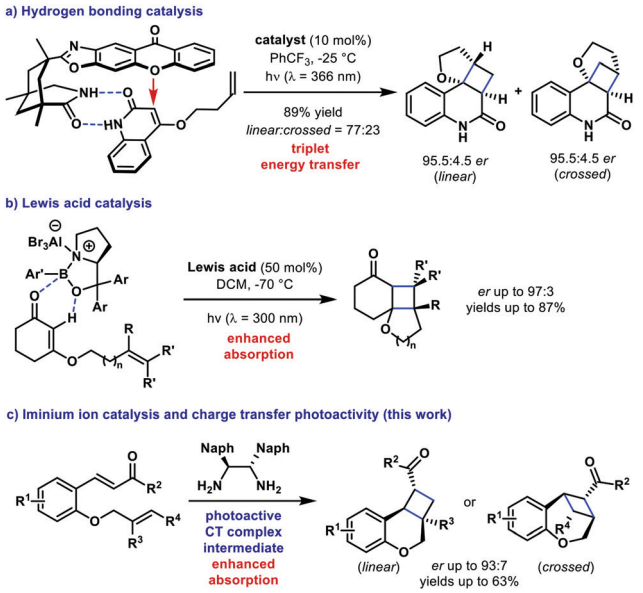
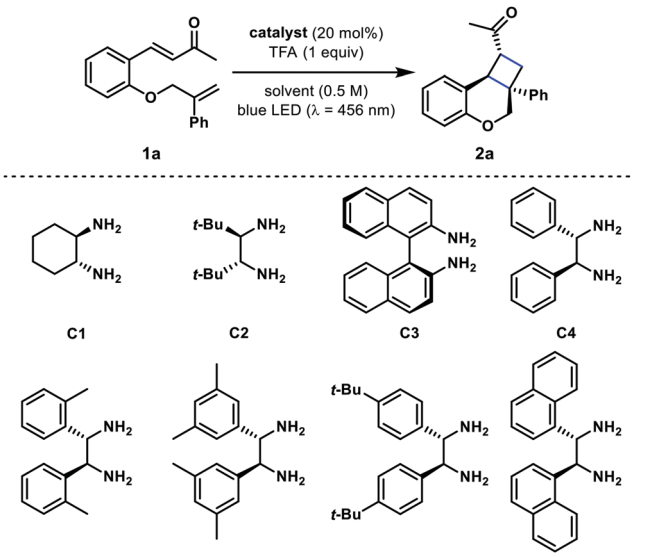



Scheme 1 Enantioselective [2+2] photocycloaddition approaches for the construction of enantioenriched polycyclic ethers.

photocycloaddition of enones bearing an O-tethered alkene moiety for the synthesis of enantioenriched tricyclic ethers through an aminocatalytic strategy enabled by the enhanced absorption observed upon formation of an electron donor–acceptor (EDA) or CT complex (Scheme 1c).

The targeted model substrate **1a** was easily synthesized by allylation of salicylaldehyde and subsequent aldol reaction with acetone. We started to investigate the intramolecular [2+2] photocycloaddition of **1a** employing a 20 mol% catalyst loading, 1 equivalent of trifluoroacetic acid and diethyl ether as the solvent under blue LED irradiation (Table 1). As expected, the use of catalysts **C1-2** (entries 1 and 2) predictably led to a negligible conversion due to the lack of a suitable donor in their structure that could unlock the formation of an intramolecular CT complex (*vide infra*). Catalyst **C3** was not effective either, leading to a low conversion (entry 3). On the other hand, employing the enantiopure diamine **C4** we were able to obtain the desired tricyclic compound in 38% yield and moderate enantioselectivity (73 : 27 er, entry 4). Thus, we studied the effect of various substitutions on the aryl scaffold (catalysts **C5-8**, entries 5–8) to increase the steric hindrance provided by the organocatalyst with the aim of achieving a higher stereoinduction. The best result was accomplished by catalyst **C8**, bearing 1-naphthyl substituents as the aryl moieties, obtaining the targeted cyclobutane in 52% yield and 83 : 17 er. As highlighted by the corresponding control experiments both the organocatalyst and light were crucial to obtain the desired product (entries 11 and 12), confirming the required mediation of an iminium ion and the photocatalytic nature of the [2+2] cycloaddition. Although only a moderate yield is obtained, due to the evidenced degradation of both starting material and product under the reaction conditions (see the ESI,† for details), it should be highlighted that during this process a tricyclic product with three chiral centers (one of which is a quaternary stereocenter) and only one diastereoisomer (dr > 98 : 2) is achieved.

Table 1 Optimization of the [2+2] photocycloaddition (selected examples)[a]

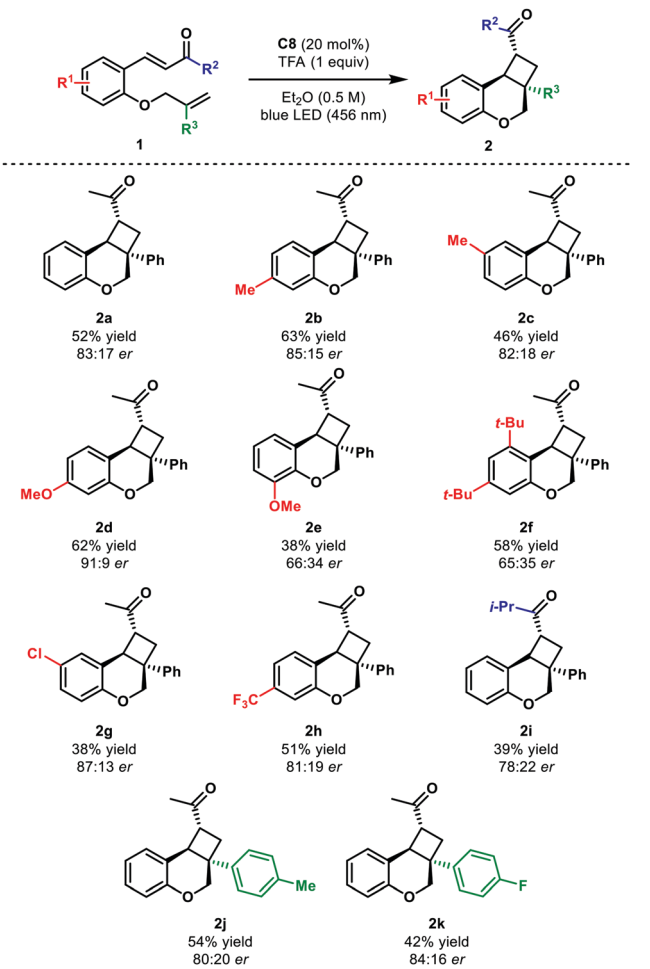



| Entry | Catalyst | Solvent | Conversion (%) | er |
|---|---|---|---|---|
| 1 | **C1** | Diethyl ether | 7 | — |
| 2 | **C2** | Diethyl ether | 0 | — |
| 3 | **C3** | Diethyl ether | 5 | — |
| 4 | **C4** | Diethyl ether | 100 | 72 : 27 |
| 5 | **C5** | Diethyl ether | 90 | 75 : 25 |
| 6 | **C6** | Diethyl ether | 93 | 71 : 29 |
| 7 | **C7** | Diethyl ether | 92 | 79 : 21 |
| 8 | **C8** | Diethyl ether | 100 (52)[b] | 83 : 17 |
| 9 | **C8** | MeCN | 50 | 83 : 17 |
| 10 | **C8** | DMSO | 0 | — |
| 11 | — | Diethyl ether | 0 | — |
| 12 | No light | Diethyl ether | 0 | — |

[a] The conversion was determined by $^1$H NMR analysis of the crude mixture after 15 h. The er was determined by chiral SFC analysis of the isolated product. [b] Isolated yield.

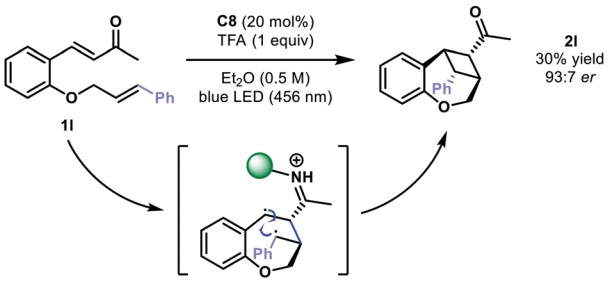
Firstly, we decided to study the effect of the substitution of the aryl group of the salicylaldehyde core. The reaction of substrates with moderate electron-donating substituents, in *para*- and *meta*-positions to the enone double bond ($R^1$ = 4-Me, 5-Me), afforded the corresponding cyclobutanes **2b** and **2c** in 63% and 46% yields and with 85 : 15 and 82 : 18 er, respectively (Table 2). The presence of a strong electron-donating substituent in the *para*-position ($R^1$ = 4-MeO) had a beneficial impact on the enantioselectivity, obtaining compound **2d** in 62% yield and 91 : 9 er. On the other hand, the employment of enones **1e** or **1f**, bearing a methoxy group in the 3-position (3-MeO) or a bulky *tert*-butyl group in the 6-position (4,6-di-*t*-Bu), afforded products **2e** and **2f** in 38% and 58% yields but with strongly diminished stereoinduction (66 : 34 and 65 : 35 er, respectively). This suggests that the *ortho*-substitution is not well tolerated. The use of enones with electron-withdrawing groups ($R^1$ = *m*-Cl, *p*-$CF_3$) led to the obtainment of products **2g** and **2h** in 38% and 51% yields and with 87 : 13 and 81 : 19 er, respectively. Enone **2i**, bearing a branched alkyl chain at the α-carbonyl position of the ketone

Table 2 Scope of the intramolecular [2+2] photocycloaddition




($R^2$ = i-Pr), provided the desired product in 39% yield and 78 : 22 er. Finally, different aryl substitutions in the O-tethered styrene moiety were tolerated. The employment of enones **1j** and **1k** ($R^3$ = *p*-Me–$C_6H_4$, *p*-F–$C_6H_4$) led to the obtainment of the corresponding cyclobutanes in moderate yields (54% and 42%) and enantioselectivity (80 : 20 and 84 : 16 er).

Furthermore, we wondered if a different substitution pattern at the alkene double bond could be tolerated (Scheme 2), using **1l** as a starting material. In this case, we were delighted to obtain the corresponding and interesting crossed seven-membered ring product **2l** with high stereocontrol (93 : 7 er) and as a single diastereoisomer (dr > 98 : 2). Indeed, as expected, the inverse regioselectivity for the cyclobutane ring formation (confirmed by 2D-NMR experiments, see the ESI†) is due to the generation of the more stable diradical intermediate upon formation of the first C–C bond of the [2+2] photocycloaddition, which, in this case, is favouring a dibenzylic diradical (*vide infra*). The absolute configuration of the tricyclic products was obtained by circular dichroism of **2d** (see the ESI†) and also in comparison with the one observed in the corresponding intermolecular reaction, which was supported by X-ray analysis.[14]




Scheme 2 Intramolecular [2+2] photocycloaddition to obtain an enantioenriched seven-membered ring polycyclic ether scaffold.

The proposed mechanism of the intramolecular [2+2] photocycloaddition is based on our previous studies,[14] and is supported by UV-Vis absorption measurements, which highlighted the formation of an iminium ion-based CT complex intermediate upon addition of catalyst **C8** (Fig. 2a). On the other hand, the use of catalyst **C1** did not lead to the formation of a photoactive intermediate due to the lack of a suitable donor moiety in its structure. The proposed mechanism (Fig. 2b) starts with the acid-promoted condensation of catalyst **C8** with enone **1a** to form the iminium ion intermediate **I**, which due to the contiguous presence of a suitable donor (naphthyl) and a suitable acceptor (iminium ion) gives a coloured ground state CT complex. Under blue LED irradiation the intermediate **I** can reach the CT excited state **II** by an intramolecular single electron transfer (SET) from the donor moiety to the transient generated acceptor fragment. The excited state **II** is an unproductive species for the photocycloaddition since its reaction would lead to a regioisomer that has not been experimentally observed.[16] Thus, the formation of this species is only triggering the excitation process due to the appearance of a new CT band that allows the excitation of an otherwise not photoactive chiral iminium ion under visible light irradiation. Therefore, **II** can restore the ground state CT complex by back electron transfer (BET) or lead to an excited species **III** by means of a thermal equilibrium in the excited state.[17] Once populated, the iminium-localized excited species **III** can react intramolecularly with the O-tethered alkene chain *via* a [2+2] photocycloaddition to give the cyclobutyl iminium ion **IV**, and furnishing the desired cyclobutane **2a**.[18]

In conclusion, we have developed an intramolecular [2+2] photocycloaddition enabled by the photoactivity of an iminium ion-based intramolecular CT complex. The excitation of a chiral intermediate was achieved without provoking a racemic background reaction of the enone, unlocking a stereoselective transformation which furnished the corresponding enantioenriched cyclobutanes. Upon visible light irradiation a CT excited state is obtained, which allows the population of an iminium-localized excited state by means of a thermal equilibrium in the excited state.

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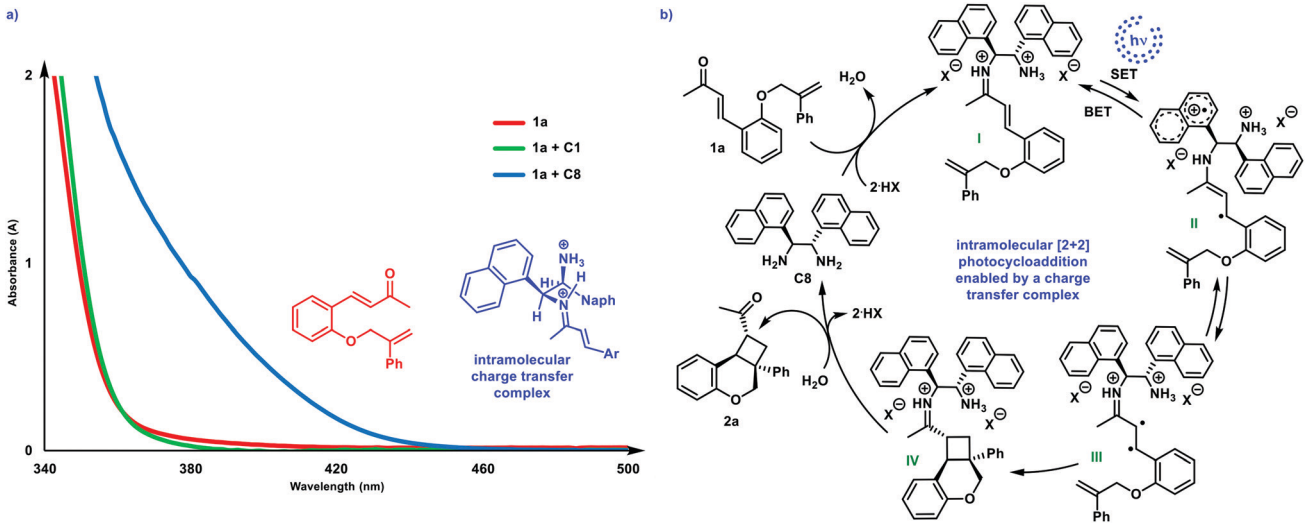


Fig. 2 UV-Visible absorption spectra (a) and the corresponding mechanistic proposal for the intramolecular [2+2] photocycloaddition (b).

All authors have given approval to the final version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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