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Enantioselective Aminocatalytic [2+2] Cycloaddition through Visible Light Excitation

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ABSTRACT. An asymmetric aminocatalytic activation strategy to obtain enantioenriched cyclobutanes through [2+2] photocycloaddition under visible light irradiation is presented. This metal-free process does not require the use of any external photocatalyst, as it is catalyzed by a simple diamine, which upon condensation with an enone substrate, forms an iminium ion intermediate that absorbs in the visible light region. The direct excitation of such an intermediate leads to a charge transfer (CT) excited state that can undergo a stereocontrolled intermolecular photocycloaddition with good enantiomeric and diastereoisomeric ratios and high yields. Finally,

DFT calculations and experiments were performed to support the charge transfer behavior and the mechanistic proposal.

INTRODUCTION

Visible light photocatalysis has received growing interest during the last decades because of its ability to achieve bond constructions that are generally not feasible using conventional and established thermal catalysis.¹ Nevertheless, enantioselective photocatalysis has found limited applications because the achievement of high levels of stereoinduction have been obstructed by various factors that are intrinsic to the nature of photochemical reactions.² Indeed, the high reactivity of open-shell intermediates and the low energy barrier of short-lived electronic excited states leads to a rapid evolution of the reaction course, challenging the possibility of a triggered and stereocontrolled transformation induced by a chiral catalyst. Additionally, the presence of non-catalyzed background racemic processes has further complicated the achievement of this goal.

In this context, the [2+2] photocycloaddition represents a powerful multiple bond construction approach for the synthesis of chiral cyclobutanes in a single step. However, despite their abundance in natural product backbones, and their importance as synthetic intermediates only a few enantioselective photocatalytic strategies to achieve enantioenriched cyclobutanes have been described to date.³ The pioneering works of Bach's group^{4,5} on catalytic enantioselective [2+2] photocycloadditions employed different strategies to achieve stereoinduction. Lactam hydrogen bonding interactions were used as a stereocontrol element, leading to a preferential energy transfer towards the catalyst-coordinated substrate (Figure 1a).^{2e,4} A second strategy relied on the exclusive photoexcitation of a chiral oxazaborolidine Lewis acid-substrate complex due to a bathochromic

absorption shift observed upon coordination.⁵ In this regard, the first intermolecular enantioselective [2+2] reaction enabled by a Lewis acid-catalyzed triplet energy transfer has been reported,⁶ whereas a chiral-at-rhodium complex has been employed to efficiently promote the [2+2] photocycloaddition over acyclic compounds (Figure 1b).⁷ Therefore, we hypothesized whether another catalytic activation mode might be feasible to obtain enantioenriched cyclobutanes derivatives, overcoming the requirement of a bidentate coordination for the substrate, as in the reported strategies (Figure 1a-b).⁴⁻⁷ Indeed, the achievement of an enantioselective [2+2] photocycloaddition over simple acyclic unfunctionalized enones is still an elusive topic due to the reactivity limitations of dual-catalytic photoredox approaches and limited reported activation modes to provide the stereocontrol.³

For this purpose, we envisioned that iminium ion catalysis could provide a suitable activation of simple unfunctionalized acyclic enones. Only two substrate-specific examples of stereoinduced photocycloaddition over iminium ions have been reported by Mariano's and Bach's groups, using UV light or an external ruthenium photosensitizer, respectively.^{8,9} Nevertheless, both approaches required pre-formation of a stoichiometric iminium ion by condensation of a chiral amine, which is merely acting as a chiral auxiliary. The development of a catalytic version of Mariano's strategy is obstructed by the fact that enones have an $n-\pi^*$ transition bathochromically shifted in comparison with the $\pi-\pi^*$ transition of an iminium ion, leading to an almost impossible selective excitation of a catalytic iminium ion and provoking a racemic background reaction of the enone.⁹ Therefore, we considered the possibility of taking advantage of the possible appearance of a new absorption band upon formation of a charge transfer (CT) complex in the excited state between an electron poor fragment ($\text{C}=\text{NH}^+-\text{CH}_n-\text{Ar}$) and an electron rich moiety ($\text{C}=\text{NH}^+-\text{CH}_n-\text{Ar}$) present in the iminium ion intermediate. Although charge transfer behavior has been elegantly employed

for enantioselective photo-redox reactions,¹⁰ its catalytic employment in intermolecular [2+2] photocycloadditions remains unexplored.^{10g} Therefore, the exploitation of iminium ion catalysis and charge transfer photoactivity seemed to be a novel complementary alternative for the synthesis of enantioenriched cyclobutanes via [2+2] photocycloaddition starting from standard acyclic enones.

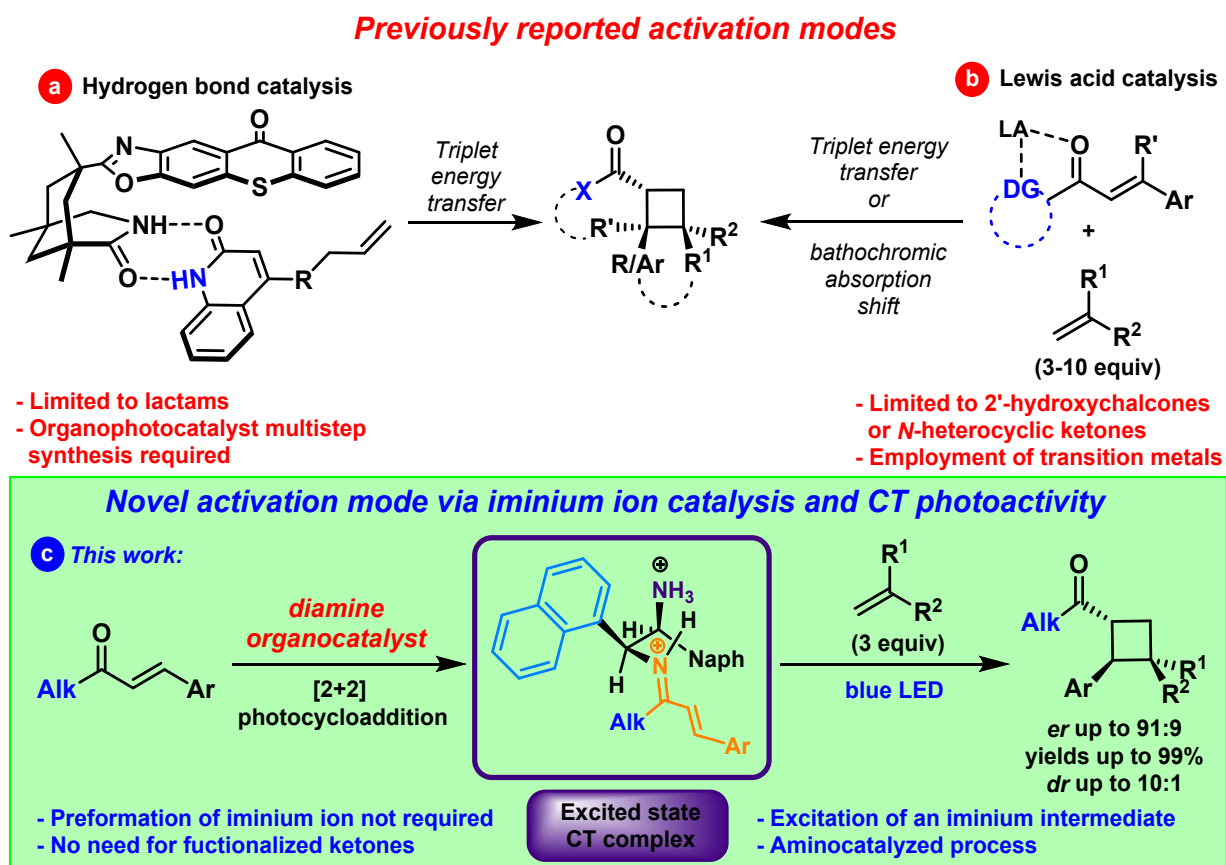


Figure 1. Enantioselective catalytic activation strategies in [2+2] photocycloadditions: a-b) previous and c) present work (Naph= Naphthyl, DG= directing group, LA= Lewis Acid, CT= Charge Transfer).

Herein we disclose the first enantioselective aminocatalytic activation strategy to obtain cyclobutanes through a stereocontrolled [2+2] photocycloaddition by the irradiation of an iminium

intermediate (Figure 1c). We found that this reaction can be applied to a variety of unfunctionalized acyclic enones and different double bonds with good yields and good enantiomeric and diastereoisomeric ratios. In addition, we have proven by mechanistic experiments that the reaction is catalyzed by a simple diamine through the direct excitation of an iminium ion intermediate triggered by the red shift absorption of a transient intramolecular charge transfer.

RESULTS AND DISCUSSION

In search of an aminocatalytic activation strategy for the development of an enantioselective [2+2] photocycloaddition, we envisioned that the *in situ* generation of an intramolecular iminium ion-based Electron-Donor-Acceptor (EDA) complex could have permitted the preferential visible light excitation of this intermediate over the carbonyl species, avoiding any racemic background process. In addition, the recently reported photoactivity of intramolecular charge transfer complexes for single-electron transfer (SET) reactions encouraged us to evaluate a new activation mode for the development of an enantioselective [2+2] photocycloaddition.^{10d,h} Taking advantage of this bathochromic shift in the visible light region (see below), the excitation of the transient iminium species would lead to an excited state chiral intermediate which could carry out a stereocontrolled [2+2] photocycloaddition. (*E*)-4-Phenyl-3-buten-2-one **1a** was chosen as a model substrate (Table 1) to obtain an enantioenriched cyclobutane **4a** that is not possible to achieve employing the previously reported catalytic activation strategies.³⁻⁷ Gratifyingly, we achieved the product of interest employing diene **2a** (3 equiv), a diamine catalyst **3a** (0.4 equiv) and TFA (trifluoroacetic acid, 1 equiv) as an acid promoter while running the reactions in acetonitrile under blue LED irradiation (Table 1, entry 1).

Table 1. Optimization studies for the [2+2] photocycloaddition.

Reaction scheme showing the [2+2] photocycloaddition of 1a (0.1 mmol) and 2a (3 equiv) to form 4a. Conditions: catalyst 3 (20 or 40 mol%), TFA (1 equiv), solvent (0.5 M), blue LED (456 nm).

Chemical structures of catalysts 3a through 3h are shown in a green box:

- 3a: Diphenylethylene diamine (DPEN)
- 3b: Mono-benzylated DPEN
- 3c: Di-benzylated DPEN
- 3d: Fluorenyl-ethylenediamine
- 3e: Anthracene-9,10-diamine
- 3f: 1,1'-bis(4-methoxyphenyl)ethylenediamine
- 3g: 1,2-diaminocyclohexane
- 3h: 2-aminobenzylamine

Entry	Catalyst (mol%)	Solvent	Conversion ^a (%)	Isolated Yield (%)	<i>er</i> ^b
1	3a (40)	MeCN	27	26	73:27
2	3b (40)	MeCN	19	17	63:37
3	3c (40)	MeCN	8	6	51:49
4	3d (40)	MeCN	53	50	80:20
5	3e (40)	MeCN	21	18	72:28
6	3f (40)	MeCN	45	45	71:29
7	3d (20)	Et₂O	100	99	90:10
8 ^c	3d (20)	Et ₂ O	0	-	-
9	-	Et ₂ O	9	-	-
10 ^d	3d (20)	Et ₂ O	100	74	82:18
11	3g (20)	Et ₂ O	10	-	50:50
12	3h (20)	Et ₂ O	12	-	-

^a Determined by ¹H NMR of the crude mixture after 17h. ^b Determined by chiral SFC analysis of the isolated product. ^c Reaction carried out in the dark. ^d Reaction carried out under air.

Indeed, diphenylethylene diamine (DPEN) **3a** afforded the product with a low conversion and moderate enantiomeric ratio (*er* = 73:27, entry 1). The use of mono-benzylated and di-benzylated

catalysts **3b** and **3c** decreased the reactivity and lowered the *er* (entries 2 and 3), indicating the need for a primary diamine catalyst in order to reach higher levels of stereinduction. We then studied the effect of the stereoelectronic nature of the aromatic backbone of the catalyst testing different C_2 symmetric diamines (entries 4-6). We found that the use of 1-naphthyl as the aryl moiety (catalyst **3d**) had a beneficial impact on both reactivity, as expected with a better donor moiety for the formation of the charge transfer complex, and stereoselectivity (*er* = 80:20, entry 4). After a final screening of the reaction conditions (see the Supporting Information), cyclobutane **4a** was obtained in excellent yields and good enantioselectivity (99% yield, *er* = 90:10, entry 7) employing a 20 mol % of catalyst loading (**3d**) and diethyl ether as the solvent. Furthermore, the exclusion of light, or the organocatalyst, suppressed the reaction almost completely (entries 8 and 9). In addition, the presence of oxygen (air) did not inhibit the reaction, and full conversion was achieved under the reaction conditions (entry 10).

The different reactivity observed with the various catalysts can be explained by the presence of intramolecular charge transfer interactions between the electron-rich moiety of catalyst **3** and the transient generated electron-poor iminium ion. As an initial qualitative observation, we noticed that a colored solution was perceived upon preparation of the reaction mixtures (Figure 2, top) and their absorption spectra was recorded (Figure 2, bottom). Indeed, a 0.05 M solution of substrate **1a** and TFA showed negligible absorption in the visible light region, explaining the low conversion observed for the racemic background process (entry 9, Table 1). The use of diamine catalyst **3a** led to a small increase in the absorbance could be due to the slight generation of a pale colored charge transfer complex in the excited state.¹¹ Conversely, when electron-rich catalysts **3d-f** were employed, a strong bathochromic shift in the visible light region was observed, turning the reaction mixture bright yellow, or orange in the case of **3e** (Figure 2). In addition, as evidenced by the use

of catalysts **3g** and **3h** (which presents a naphthyl substituent as catalyst **3d**), a transient generated iminium ion, which lacks of charge transfer interactions and thus of a bathochromically shifted absorption band (the new charge transfer band), cannot be responsible for the photoactivity, leading to a negligible conversion (entries 11 and 12, Table 1 and Figure 2). This indicates that only the intramolecular charge transfer transition is responsible for the increased absorption at the irradiation wavelength (456 nm) and for the resulting photoactivity, demonstrating that the direct excitation of an iminium ion is not feasible under the reaction conditions (see the Mechanistic Section and the Supporting Information for further details).¹² All these evidences are consistent with the formation of a charge transfer complex in the excited state that can lead to the preferential excitation of the iminium intermediate over the carbonyl substrate, allowing the enantioselective reaction to proceed under visible light irradiation without the use of any external photosensitizer.

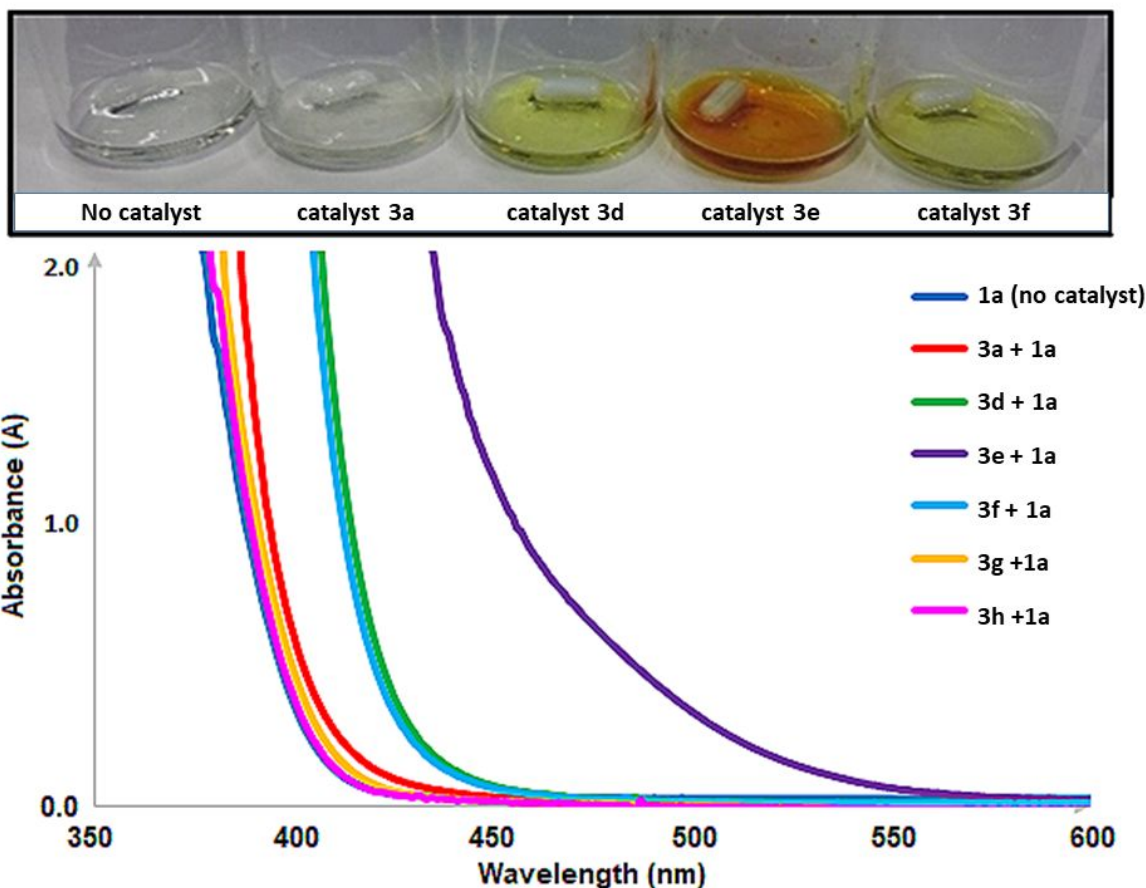
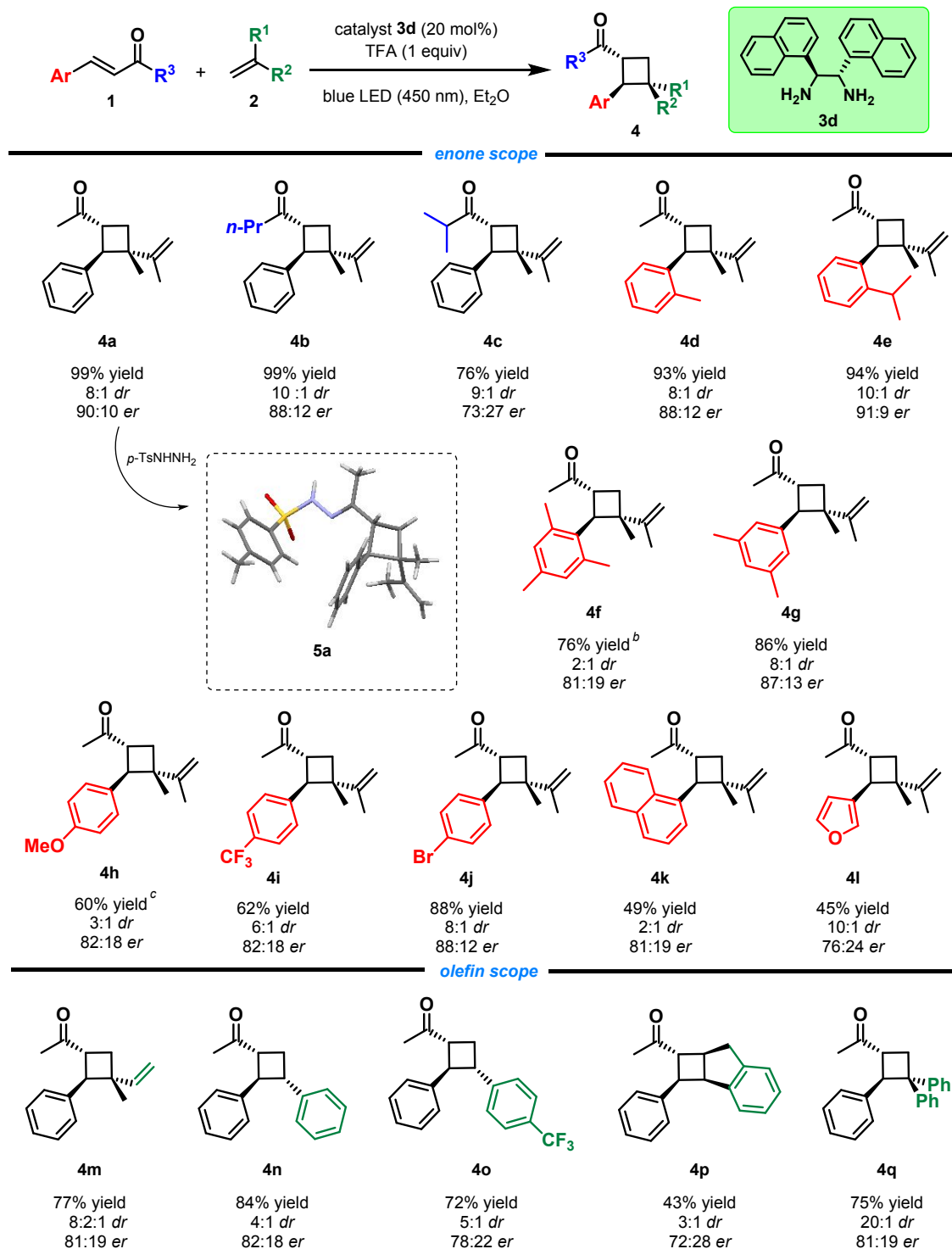


Figure 2. Top: Visual appearance of the reaction mixtures with the different catalysts. Bottom: Absorption spectra (0.05 M solutions in 1 cm quartz cell; see the Supporting Information for further details).

After optimizing the reaction conditions, we studied the scope of the reaction considering both enones **1** and alkenes **2** (Table 2). The reaction proceeded efficiently with enone **1b**, obtaining the corresponding product **4b** with a high yield and good enantioselectivity (99% yield, *er* = 88:12). Enone **1c** led to the desired cyclobutane adduct **4c**, although with slightly lower *er* values, probably due to an inefficient condensation of the primary diamine catalyst and hence, a more consistent racemic background process. The substitution on the aryl moiety was well tolerated and different cyclobutanes (**4d-j**) could be obtained using this methodology. The reaction tolerated the presence

of different *ortho* substituents at the aryl ring of the enone leading to the corresponding more sterically hindered cyclobutanes **4d-f**. Indeed, *ortho*-methyl and *ortho*-isopropyl substituents can be present in the starting enone leading to the corresponding cyclobutanes **4d** and **4e** in high yields and good enantiomeric ratios (93% yield, *er* = 88:12 and 94% yield, *er* = 91:9, respectively). Furthermore, *ortho* disubstituted and *meta* disubstituted cyclobutane **4f** and **4g** were obtained without a significant erosion in the yield and enantioselectivity (76% yield, *er* = 81:19 and 86% yield, *er* = 87:13, respectively). The presence of electron-donating (MeO-, **1h**) and electron-withdrawing (CF₃-, **1i**) groups had little impact on the reaction, isolating the products **4h** and **4i** with good enantioselectivities (60% yield, *er* = 82:18 and 62% yield, *er* = 82:18, respectively). The *para*-Br substituted enone **1j** led to the halogenated cyclobutane **4j** (88 % yield, *er* = 88:12), which could be further manipulated by cross-coupling methodologies. Gratifyingly, other aryl moieties such as 1-naphthyl and 3-furanyl can be introduced in the final product with comparable enantioselectivity, giving cyclobutanes **4k** and **4l**. The reaction was also tested with different olefins to prove the generality of the protocol. When isoprene was employed as the alkene partner, cyclobutane **4m** was obtained in 77% yield, while styrene proceeded smoothly to product **4n** with an 84% yield and 82:18 *er*. Electron-poor styrene **1l** led to the CF₃-containing cyclobutane **4o** with a 72% yield and 78:22 *er*. The employment of indene led to the formation of cyclobutane **4p**, which contains an interesting tricyclic scaffold. On the other hand, the quaternary carbon-containing product **4q** could be obtained with a 75% yield when 1,1-diphenylethylene was employed as the olefin partner. In addition, although a partial *E/Z* isomerization of enone **1** was normally taking place during the progress of the reaction, as evidenced by ¹H NMR analysis, this did not show a remarkable effect on the reaction outcome, even if it surely represents an operative dissipating pathway for this process. Indeed, when (*Z*)-4-phenyl-3-buten-2-one was employed as

the enone substrate we were delighted to notice that we exclusively obtained cyclobutane **4a** (84% yield and 80:20 *er*), due to an organocatalyzed equilibration of the *Z* isomer to the more stable *E* isomer.¹³ Moreover, unfortunately, the employment of an enone bearing an aliphatic substituent at the β -position did not lead to the obtainment of any cyclobutane, neither when we changed the irradiation source to shorter wavelengths (UV LED) to ensure the absorption of the photons by the reaction mixture, probably due to vibrational deactivation by energy dissipation of the corresponding excited state.^{3a} The absolute configuration of the enantioenriched cyclobutanes **4** was determined by derivatization of **4a** to hydrazone **5a**, which was unambiguously confirmed by single crystal X-ray crystallography (See Table 1 and the Supporting Information for further details).¹⁴

Table 2. Scope of the reaction in the [2+2] photocycloaddition^a

^aReaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), **3d** (0.02 mmol), TFA (0.1 mmol) and 0.2 mL of Et₂O (see the Supporting Information for further details). ^b0.9 mmol of **2** were employed. ^cMTBE used as the solvent.

MECHANISTIC PROPOSAL

The proposed reaction mechanism (Figure 3) would start with the acid-promoted condensation of diamine catalyst **3d** with enone **1a** to form the iminium ion intermediate **A-1**, which due to the contiguous presence of donor (naphthyl) and acceptor (iminium ion) moieties, can give a colored intermediate as a consequence of formation of a charge transfer complex in the excited state. The latter can reach, upon blue LED irradiation, the excited state **B-2**. Indeed, from the ground state **A-1**, a SET between the donor and the acceptor moieties can give an unproductive excited state **B-2**,¹⁵ that would successively restore **A-1** by BET (back electron transfer) or lead to an excited species **B-1** by means of a thermal equilibrium in the excited state (*vide infra*).^{10e-f} Furthermore, the singlet excited state species **B-1** can react with alkene **2a** in a [2+2] photocycloaddition to give the biradical intermediate **C-1**.^{8,16,17} The latter evolves to the cyclobutyl iminium ion **D-1**, which after hydrolysis, gives the cyclobutane product **4a** and catalyst **3d**.

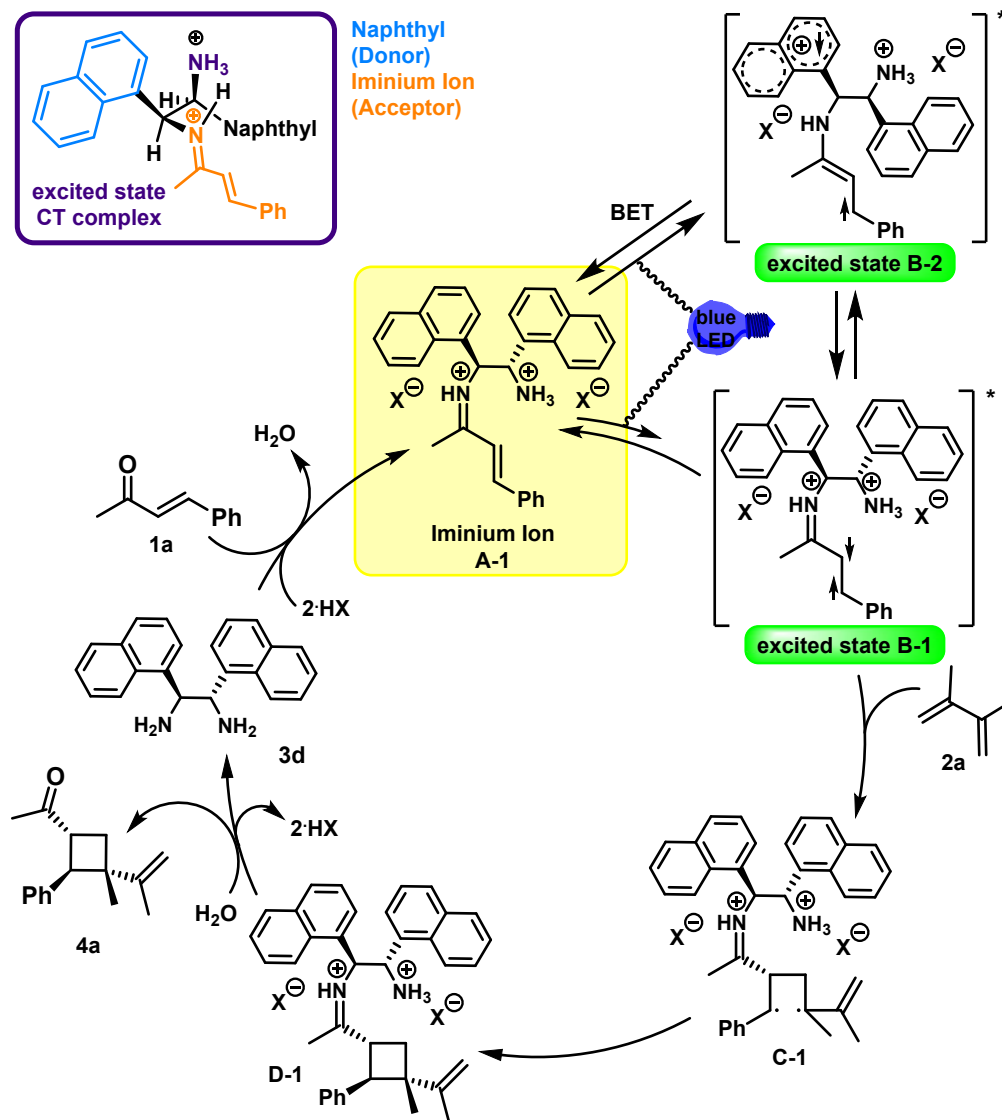


Figure 3. Mechanistic proposal for the [2+2] photocycloaddition via intramolecular CT complex in the excited state.

The singlet excited state reactivity is in accordance with the examples of [2+2] photocycloadditions over stoichiometric iminium ions that were reported by Mariano's research group.^{8,16c} In addition, when the reaction was performed employing the triplet photosensitizer $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ (0.2 mol%) the reaction could be further catalyzed by triplet energy transfer (Figure 4).^{6a-b,9,18} Under these conditions, the stereochemical outcome (diastereoisomeric ratio) of

the reaction was significantly different from the singlet pathway that we have proposed, since an excited triplet iminium ion induced by the metal photocatalyst is supposed to be the reactive species. Indeed, the diastereoisomeric ratio observed in product **4k** ($dr = 5:1$) upon triplet photosensitization was significantly different from the one observed in the absence of the ruthenium photosensitizer ($dr = 2:1$) because of the different nature of the excited intermediates (Figure 4). Product **4k** was properly chosen for this comparison because of the low dr obtained without an external photocatalyst (Table 2). The different diastereoisomeric ratios observed in the two cases are in accordance with the different reaction mechanism (Figure 4). The triplet pathway is a stepwise mechanism whereas the singlet pathway can be a stepwise or a concerted mechanism.^{3a} The important difference is that the triplet biradical is supposed to exist for a longer time since it is necessary for it to undergo an intersystem crossing (ISC) to a singlet state before being able of forming the second C-C bond of the cyclobutane ring. Thus, the different lifetime of this intermediate is responsible of the higher diastereoisomeric ratio observed, since it is easily understandable that a longer lifetime can permit a higher degree of organization of the biradical to place the bulkier substituent (*i*-propenyl) *trans* to the aromatic substituent (naphthyl) of the cyclobutane ring.

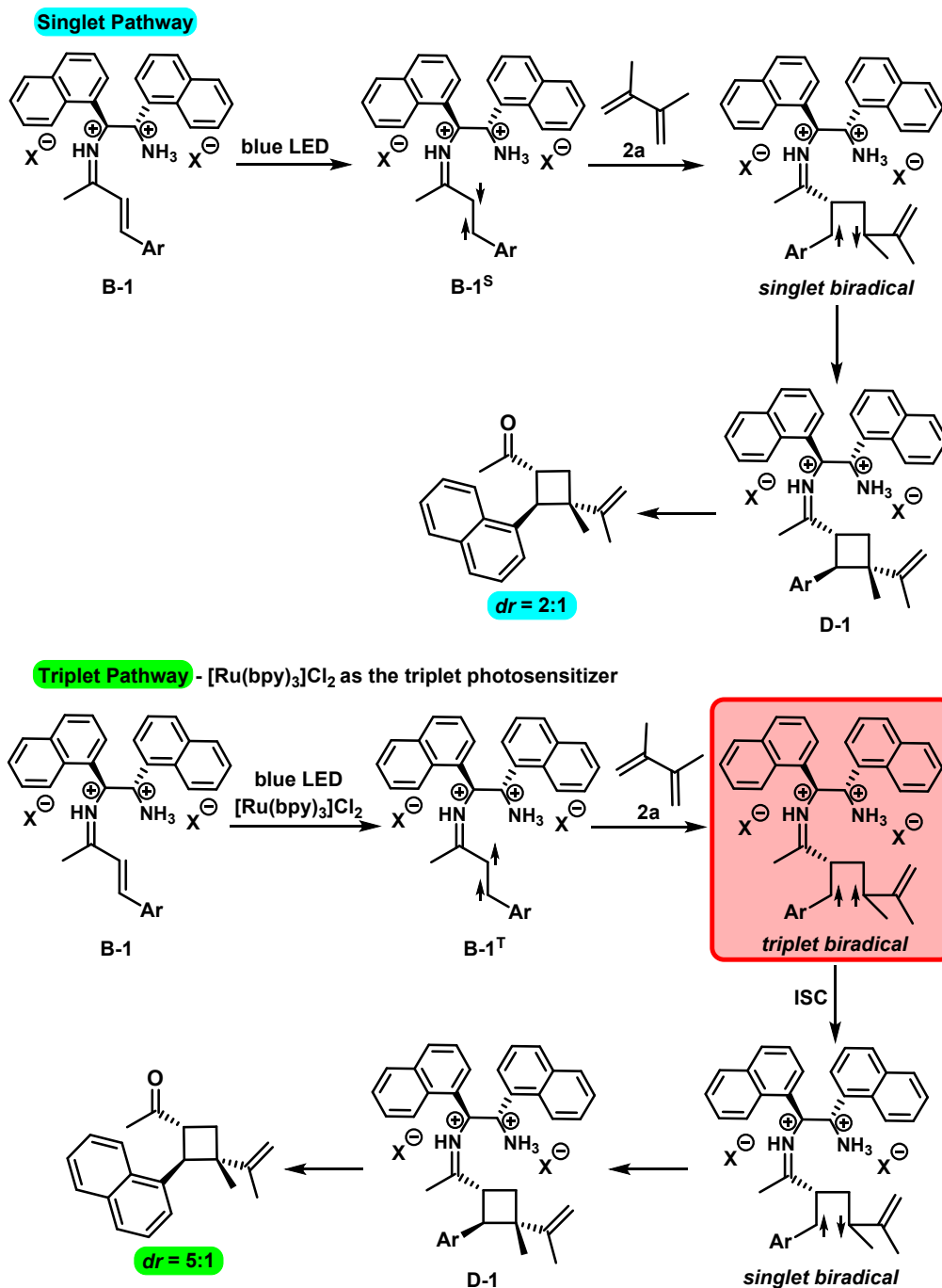


Figure 4. Different diastereoselectivity of singlet and triplet mechanisms.

In order to provide further insights into the molecular and electronic structures of the iminium ion formed upon condensation of enone **1a** and catalyst **3d** (**A-1**, Figure 3), DFT calculations at the M062X/6311G** level were performed. We thoroughly explored the potential energy surface,

and different conformations have been isolated as local minimums (see the Supporting Information). However, as a consequence of the inherent geometric constrictions of the molecule considered, none of the conformers found included π -stacking between the naphthyl moiety and the iminium fragment. Nevertheless, the intramolecular CT behavior is suggested from the analysis of the electronic structure of the more stable conformer, which indicates that the HOMO orbital is located in one of the naphthyl moieties and the corresponding LUMO is found in the iminium fragment (Figure 5, top).^{10h,19} Therefore, excitation of this intermediate can lead to an intramolecular single-electron transfer from the naphthyl to the iminium moiety. Indeed, optimization of the same structure in the triplet spin state at the same calculation level indicates that the SOMO orbitals correspond exactly to the HOMO and LUMO orbitals found in the singlet spin state (see the Supporting Information). Furthermore, we analyzed the possible electronic transitions by means of single point TDDFT calculations (CAMB3LYP/631G*) on the optimized structure at the M062X/6311G** level (Figure 5, top). Indeed, the first allowed $S_0 \rightarrow S_1$ transition is found at approximately 380 nm and it is mainly described as an internal single electron transfer from the HOMO in one of the naphthyl moieties to the LUMO in the iminium fragment.^{10h,19}

Although the intramolecular CT behavior is suggested from the DFT analysis, the lower energy singlet charge transfer excited state (**B-2**) cannot be responsible for the reaction outcome.¹⁵ In fact, a singlet excited state with two unpaired electrons in the iminium fragment (**B-1**) is expected to be the active species in the [2+2] photocycloaddition observed.^{8,16} Interestingly, further analysis of our TDDFT data reveals that we can expect a more intense second $S_0 \rightarrow S_2$ transition found at close energy from the first transition (350 nm). This second transition is mainly described as a HOMO-3/LUMO excitation, as both involved orbitals are localized on the iminium fragment. This excited state (**B-1**) is supposed to produce the biradical species **C-1**, which has also been studied by DFT

calculations at the M062X/6311G** level at both triplet and open-shell singlet spin states. Remarkably, the **C-1** species is 20.6 kcal/mol more stable than the other biradical species that could putatively be formed from a charge transfer excited state **B-2** (**C-1'**; Figure 5, bottom). Therefore, as expected, excited state **B-1** is suggested to be the reactive species in the [2+2] photocycloaddition. Open-shell singlet species **C-1** can be located as a local minimum in the potential energy surface, however, it readily evolves exothermically (-30.3 kcal/mol) to the postulated cyclobutane intermediate **D-1** through a very shallow kinetic barrier (<1 Kcal/mol).

The combination of the experimental results and theoretical data suggests that although intramolecular charge transfer behavior is observed for **A-1**, the CT species is unproductive for the reaction. Indeed, the reaction should proceed from an iminium-localized singlet excited state that appears close in energy to the charge transfer transition. In order to study the role of the naphthyl group at the iminium ion for the charge transfer behavior, we optimized the structure of an **A-1** analogue but replacing the naphthyl fragments by methyl groups (see the Supporting Information). According to the theoretical results, we should expect an intense first $S_0 \rightarrow S_1$ transition at 353 nm, which essentially corresponds to the $S_0 \rightarrow S_2$ transition for compound **A-1**. Therefore, the appearance of a new absorption band in the visible light region, due to the iminium ion **A-1**, enables its excitation to the CT excited state **B-2** at longer wavelengths, which can convert through a thermal equilibrium to the iminium-localized singlet excited state (**B-1**).^{10e-f} Once the iminium-localized singlet excited state has been populated, the stereocontrolled [2+2] photocycloaddition can be carried out.

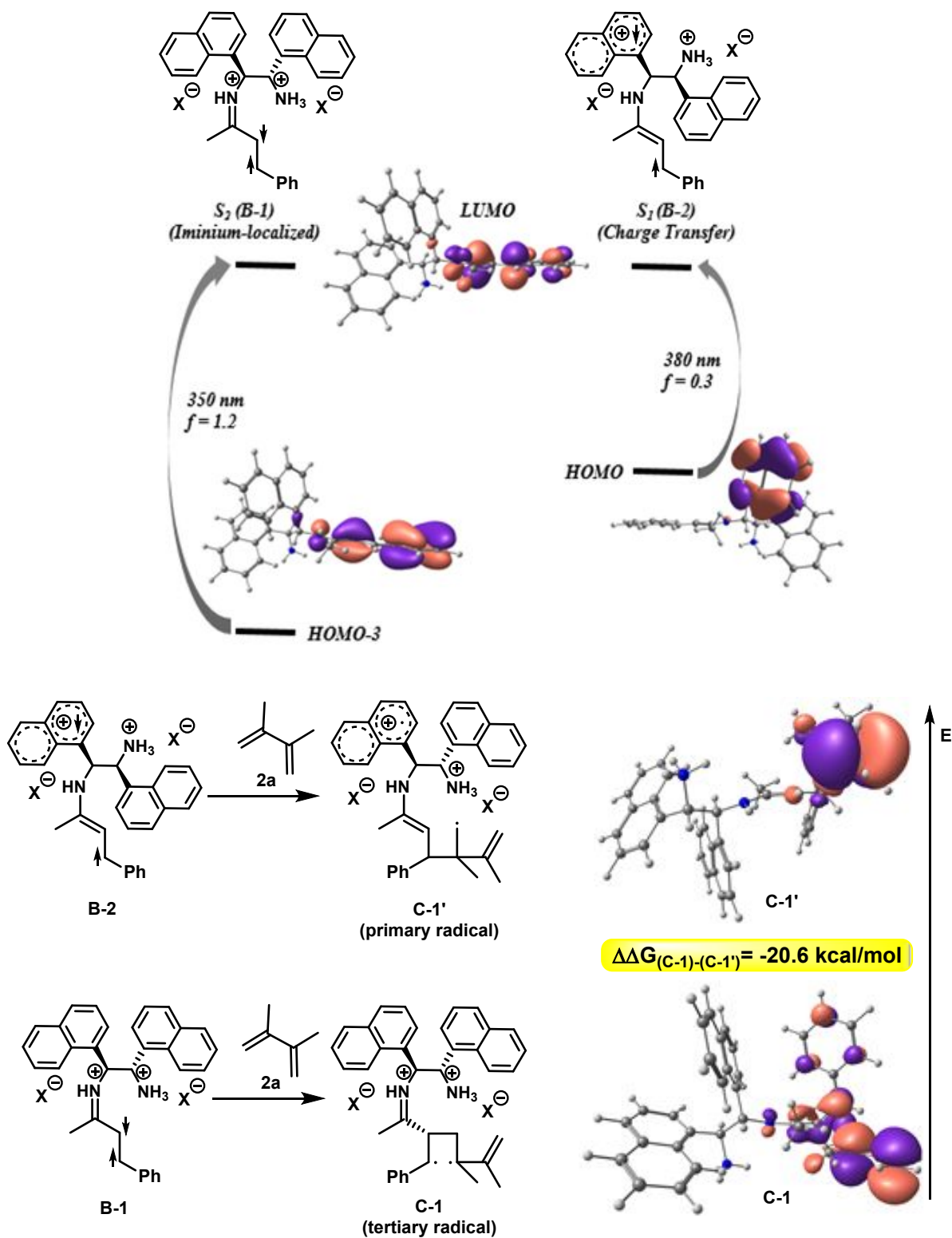


Figure 5. Top) $S_0 \rightarrow S_1$ and $S_0 \rightarrow S_2$ transitions found from TDDFT calculations at the CAMB3LYP/631G* level on the optimized structure at M062X/6311G** level of the A-1 species.

The orbitals found at the M062X/6311G** level are drawn at 97% probability. Bottom) Two possible pathways leading to the experimentally observed product and relative energy of the two corresponding radicals (SOMO-2 orbitals).

The representation of the energy diagram for the different species involved in the excitation process is illustrated in Figure 6. The iminium ion **A-1** can reach a charge transfer excited state **B-2** (singlet charge transfer, **CT^S**), which can convert to the excited species **B-1** (singlet iminium-localized, **LE^S**) by means of a thermal equilibrium in the excited state.^{10e-f,20} The presence of this equilibrium is crucial for a successful reaction to take place and, as expected, is highly solvent dependent (related to the solvent dielectric constant).^{10e-f,20} Indeed, polar solvents favor the **CT^S** species while apolar solvents favor the **LE^S**, allowing the population of the iminium-localized excited state to a further extend and, as a consequence of that, observing an increased reactivity (see the Supporting Information). In principle, the singlet excited species could undergo an intersystem crossing (ISC) to the triplet analogues. However, as expected, according to El-Sayed's rule,^{16b,21} the ISC rate would be extremely slow for an iminium-ion, discarding any contribution of triplet excited species in this system. Therefore, the singlet iminium-localized excited species **B-1** (**LE^S**) is proposed as the only active intermediate.¹⁵

The TDDFT calculations revealed that, although spin-forbidden through direct excitation, the most favorable (and lowest in energy) of the singlet-triplet transitions is localized over the iminium fragment (HOMO-3/LUMO), with an energy gap of 46 kcal/mol.¹⁷ Thus, through the use of an external ruthenium photosensitizer, the reaction can be further catalyzed by means of triplet photosensitization, populating the iminium-localized triplet excited state, as observed experimentally (see blue line, right-Figure 6).

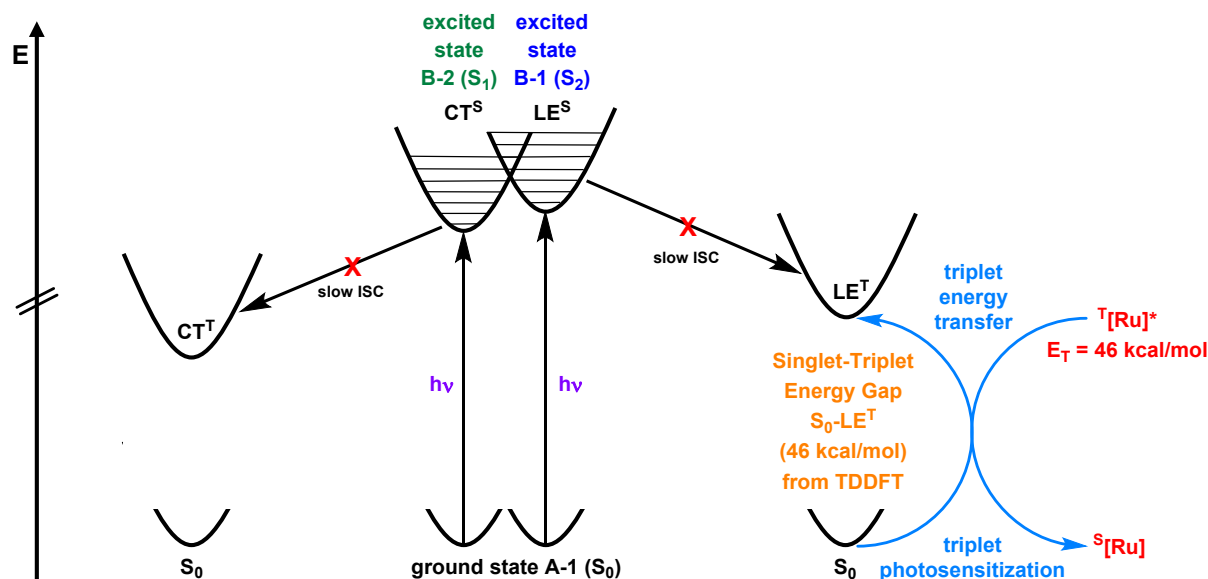
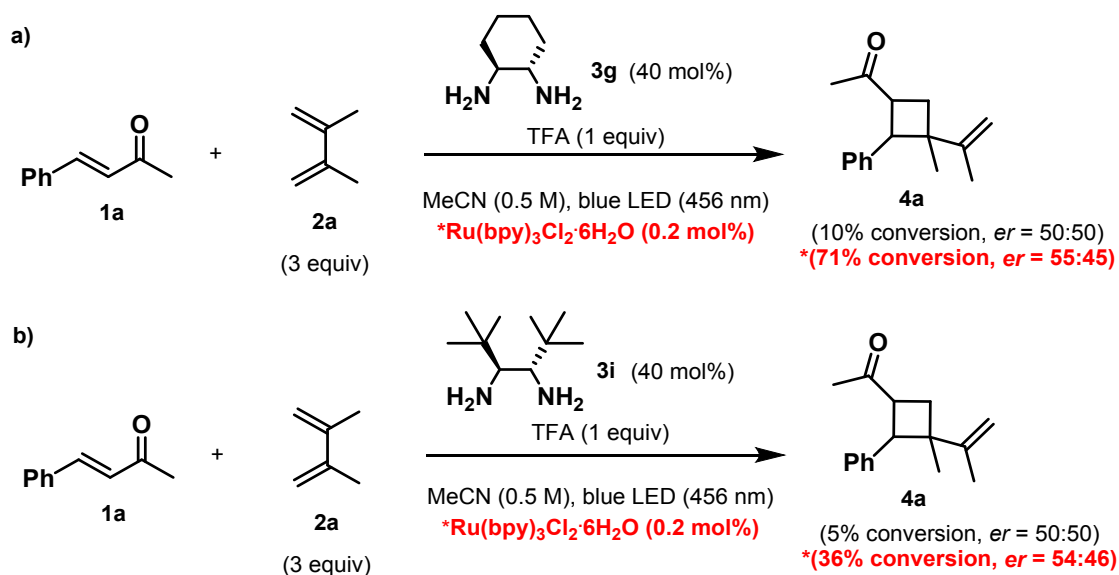


Figure 6. Representation of the energy diagram for the ground state and excited state species that are involved in the CT excited state mediated [2+2] photocycloaddition or in the triplet photosensitized analogous reaction.

To gain further evidence in support of the mechanistic proposal, some additional experiments were performed (Scheme 1). The employment of alkyl catalysts **3g** or **3i** predictably led to negligible conversion and to a racemic product since they are unable to form an intramolecular CT complex in the excited state due to the lack of electron-rich (donor) moieties (Scheme 1a,b).²² On the other hand, when a ruthenium photocatalyst was employed as an external photosensitizer the reaction was able to proceed through a triplet energy transfer mechanism, indicating that, even if not capable of forming any charge transfer complexes, catalysts **3g** and **3i** can properly condensate with enone **1a** to carry out the reaction via an iminium ion intermediate, albeit with a low enantioselectivity.^{6a-b,9,23}

Scheme 1. Additional proofs supporting the mechanistic proposal.



CONCLUSIONS

In conclusion we have described an aminocatalytic activation strategy to obtain enantioenriched cyclobutane derivatives. The direct excitation of an intramolecular charge transfer complex allows the use of visible light irradiation in the [2+2] photocatalytic cycloaddition, avoiding uncatalyzed pathways between enones and dienes, which enables an asymmetric iminium ion catalyzed reaction. The combination of the experimental data and DFT calculations reveal that the charge transfer behavior results from a low energy charge transfer excited state (**B-2**). Furthermore, such an intermediate makes accessible, through a thermal equilibrium, a localized excited state (**B-1**), which is the active species in the [2+2] cycloaddition. This is the first aminocatalytic enantioselective [2+2] reaction that enables the preparation of enantioenriched cyclobutanes, which are inaccessible by Lewis acid activation strategies reported until now.

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Author Contributions

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

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge.

Experimental details, characterization data of compounds, NMR spectra, SFC traces, mechanistic discussion and DFT calculations data (PDF)

X-Ray Crystallographic Data (CIF)

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12. This was clearly demonstrated by means of UV-Visible absorption measurements which indicated that only the intramolecular charge transfer transition is responsible for the increased absorption at the irradiation wavelength (456 nm) and for the resulting photoactivity (see Supporting Information for further details). Indeed, irradiation at the new required charge transfer absorption band is responsible for the population of an iminium-localized excited state by means of an indirect excitation pathway (see the Mechanistic Section for a detailed discussion). Although the absorption spectra of the reaction mixtures obtained employing catalysts **3g** and **3h** are the same of a TFA solution of enone **1a** (indicating that a transient generated iminium ion cannot be the photoactive species) the efficient formation of the corresponding iminium ions was confirmed by the fact that these catalysts can work in the reaction through a triplet photosensitization mechanism (see the Mechanistic Section and the Supporting Information for further details).

13. A similar organocatalyzed equilibration between the *Z* and *E* isomers of cinnamaldehyde was observed by Melchiorre's group: Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. Visible-light Excitation of Iminium Ions Enables the Enantioselective Catalytic β -Alkylation of Enals. *Nat. Chem.* **2017**, *9*, 868-873.

14. CCDC 1923032 (**5a**) contains the crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk.

15. We can discard **B-2** from being the reactive species in the [2+2] photocycloaddition because of the observed experimental regioselectivity and because of the results of DFT calculations (see the Supporting Information for a full explanation and details).

16. For examples of singlet state reactivity of iminium ions, see: (a) Brenninger, C.; Jolliffe, J. D.; Bach T. Chromophore Activation of α,β -Unsaturated Carbonyl Compounds and Its Application to Enantioselective Photochemical Reactions. *Angew. Chem. Int. Ed.* **2018**, *57*, 14338-14349; (b) Klán, P.; Wirz, J. *Photochemistry of Organic Compounds*. Wiley, Chichester, **2009**; (c) Cai, X.; Chang, V.; Chen, C.; Kim, H.-J.; Mariano, P. S. A Potentially General Method to Control Relative Stereochemistry in Enone–Olefin 2+2-Photocycloaddition Reactions by using Eniminium Salt Surrogates. *Tetrahedron Lett.* **2000**, *41*, 9445-9449.

17. A concerted [2+2] reaction in which the two C-C bonds were formed simultaneously, leading directly to cyclobutyl iminium ion **D-1**, is an alternative plausible pathway. Nevertheless, the possibility of the presence of a biradical intermediate was indicated by DFT calculations (see the Supporting Information for the details).

18. In the presence of an external photosensitizer the reaction can be further catalyzed through a triplet energy transfer mechanism. Indeed, by means of TDDFT calculations (Figure 5, see the Supporting Information for further details), the singlet-triplet energy gap for the CT complex **A-1** has been found being 46 kcal/mol which is in accordance with the triplet energy of $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ that has been reported in the literature (46 kcal/mol). On the other hand, the enone substrate **1a** presents a higher energy gap that does not allow the reaction to proceed in the absence of a diamine catalyst, which enables the formation of the iminium ion (conversion <10% without organocatalyst), and it has been supported by further experimental evidences (Scheme

1a,b). Nevertheless, the enantiomeric excesses obtained from the singlet and triplet pathways (Figure 4) were comparable, indicating once again the intermediacy of an iminium ion catalyzed reaction in both of them.

19. DFT analysis clearly indicated which one of the two naphthyl fragments is acting as the donor moiety for the formation of the EDA (or CT) complex. This explained as well why, in this case, there is no need and we do not observe any π -stacking between the donor and the acceptor moieties for the formation of the charge transfer complex. This is in accordance with the formation of intramolecular charge transfer excited species, in which there is no possibility of π -stacking interactions, that have been widely reported in the literature. For a representative example, see: Fukuzumi, S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. Electron-Transfer State of 9-Mesityl-10-methylacridinium Ion with a Much Longer Lifetime and Higher Energy Than That of the Natural Photosynthetic Reaction Center. *J. Am. Chem. Soc.* **2004**, *126*, 1600-1601. For an example of an intramolecular CT behaviour that does not require π -stacking interactions, see: ref. 10h. Furthermore, TDDFT analysis further confirmed that only one of the two naphthyl moieties is involved and responsible of the charge transfer transition ($S_0 \rightarrow S_1$ transition) that is giving, as a consequence, a new bathochromically shifted charge transfer absorption band.

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22. This suggests that the low conversion was simply due to background processes.
23. This clearly demonstrate that the iminium ion obtained from the condensation of an alkyl diamine catalyst with enone **1a** can reach a triplet excited state by triplet energy transfer from an external ruthenium photocatalyst. Indeed, by means of TDDFT calculations (see the Supporting Information), the singlet-triplet energy gap for an analogous iminium ion, unable of forming any CT complex due to the lack of naphthyl moieties (replaced by methyl groups), has been found being 46 kcal/mol which is in accordance with the triplet energy of Ru(bpy)₃Cl₂·6H₂O that has been reported in the literature (46 kcal/mol). On the other hand, the enone substrate **1a** presents a higher energy gap that does not allow the reaction to proceed in the absence of a diamine catalyst, which enables the formation of the iminium ion, leading to a negligible conversion (<10%). This is in accordance with the reported results of triplet sensitization over stoichiometric iminium ions reported by Bach's research group (see ref. 9).

GRAPHICAL ABSTRACT

