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Hydrogen-Bonding Organocatalysis Enabled Photocatalytic Intramolecular [2+2]-Cycloaddition Reaction

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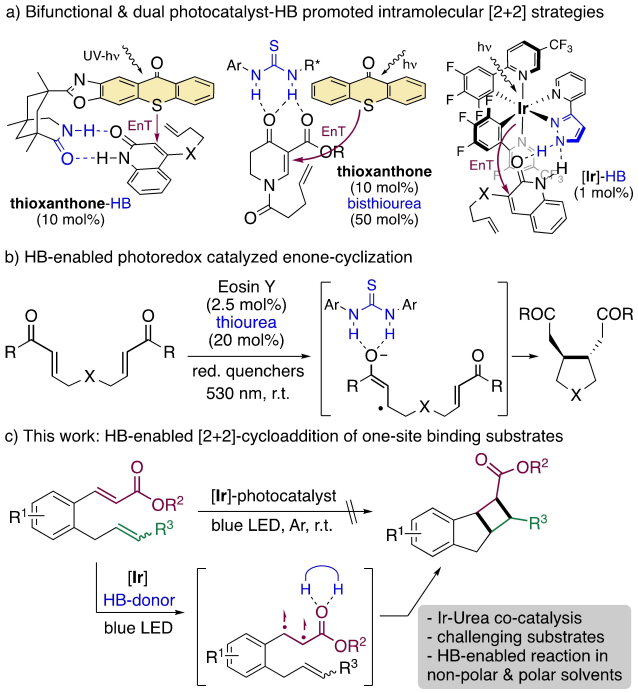
Abstract: The combination of organocatalytic activation and photocatalysis for enabling the intramolecular [2+2]-cycloaddition of enone-ene substrates bearing one Lewis base binding site is reported. While in a variety of solvents a poor conversion or no reaction takes place in the absence of a hydrogen bonding catalyst, the corresponding ring-fused cyclobutane products could be built in moderate to good yields using a synergistic dual iridium-urea co-catalytic system. Control and mechanistic studies supported the postulated interaction between the organocatalyst and the substrate, which proved essential for an efficient energy transfer from the photosensitizer.

Keywords: Photocatalysis; Hydrogen Bonding; Energy transfer; Synergistic catalysis; [2+2]-cycloaddition

The merging of organocatalytic activation[1] with photocatalysis[2] has been recently materialized as a powerful tool,[3] allowing for new reactivities and stereocontrol in challenging light-mediated processes.[4] Beside pioneering work involving covalent activation by the groups of MacMillan,[4] Rueping,[5] and Rovis,[6] Lewis acid[7] and Brønsted acid catalysis[8] have also been efficiently employed. Furthermore, less directional non-covalent hydrogen-bonding (HB)[9] interactions have also received great attention in recent years. In particular, the activation of carbonyl substrates by LUMO-lowering facilitating photoredox single electron transfer (SET) or energy transfer (EnT) processes represents a potent emerging strategy.

While intermolecular [2+2]-cycloadditions are widely investigated and constitute a benchmark reaction for the evaluation of new photocatalytic EnT systems,[10] intramolecular strategies have been less explored. In this context, Bach and co-workers exploited the enone hydrogen bonding LUMO-lowering phenomenon for the development of a few asymmetric energy transfer [2+2]-photocycloaddition approaches.[11,12] In 2009, they reported a thioxanthone triplet sensitizer bearing templating HB-donor/acceptor units to bind the complementary quinolone substrate that was operative under UV light (Scheme 1a, left).[11] This strategy proved highly efficient[12] but had some scope restrictions. Later on, the use of a bisthiourea allowed to perform the cycloaddition by multidentate HB-binding to ketoenone-type substrates (Scheme 1a, middle).[13] Moreover, Yoon and co-workers also designed an efficient bifunctional iridium photocatalyst bearing a pyrazole as HB-donor site for the binding of the substrate (Scheme 1a, right).[14] Alternatively to EnT catalysis, in 2013, the group of Zeitler reported an Eosin Y catalyzed photoredox reductive cyclization of bisenones enabled by the presence of a thiourea HB-cocatalyst (Scheme 1b).[15] More recently, the portfolio in photoredox co-catalysis involving carbonyl and

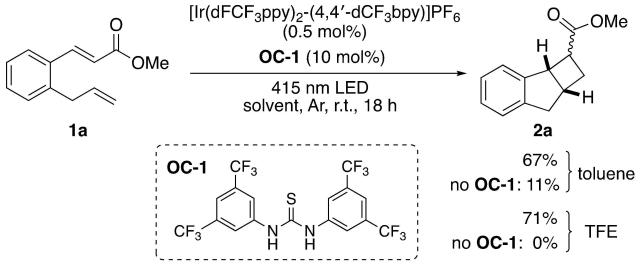


Scheme 1. Hydrogen-bonding promoted intramolecular photocatalyzed cyclizations by LUMO-lowering: a) previous [2+2] photochemical strategies, b) photoredox catalyzed bisenone reaction, and c) this approach on HB-enabled intramolecular [2+2]-cycloaddition of one-site binding carbonyl substrates.

imine HB-activation has been expanded by embracing ion pairing strategies,[16] though the beneficial effects of hydrogen bonding activation in EnT processes in terms of reactivity rather than enantioselectivity have been neglected.

Inspired by the mentioned breakthroughs and following our program on synthetic photocatalytic methods,[17] we envisioned an intermolecular [2+2]-cycloaddition triggered by HB-activation of substrates bearing only one Lewis base binding site (Scheme 1c). Hence, we present the activation of enone-ene derivatives by the combination of an iridium photocatalyst and a simple bidentate hydrogen bonding catalyst, allowing to extend the reaction media in which this process can be performed.

Initial studies with **1 a** as enone-ene model substrate using 0.5 mol% of [Ir(dFCF$_3$ppy)$_2$-(4,4′-dCF$_3$bpy)]PF$_6$, a well-known triplet energy sensitizer Ir-photocatalyst (E_T: 55.4 kcal/mol),[18] in non-polar solvents such as toluene or polar-protic solvents such as trifluoroethanol (TFE) were performed. Under blue light irradiation (415 nm LED) and argon atmosphere at room temperature (20 °C), poor or no reactivity for the [2+2]-cycloaddition was observed (Scheme 2). However, the presence of 10 mol% of the Schreiner thiourea catalyst (**OC-1**) effectively promoted the reaction. To our



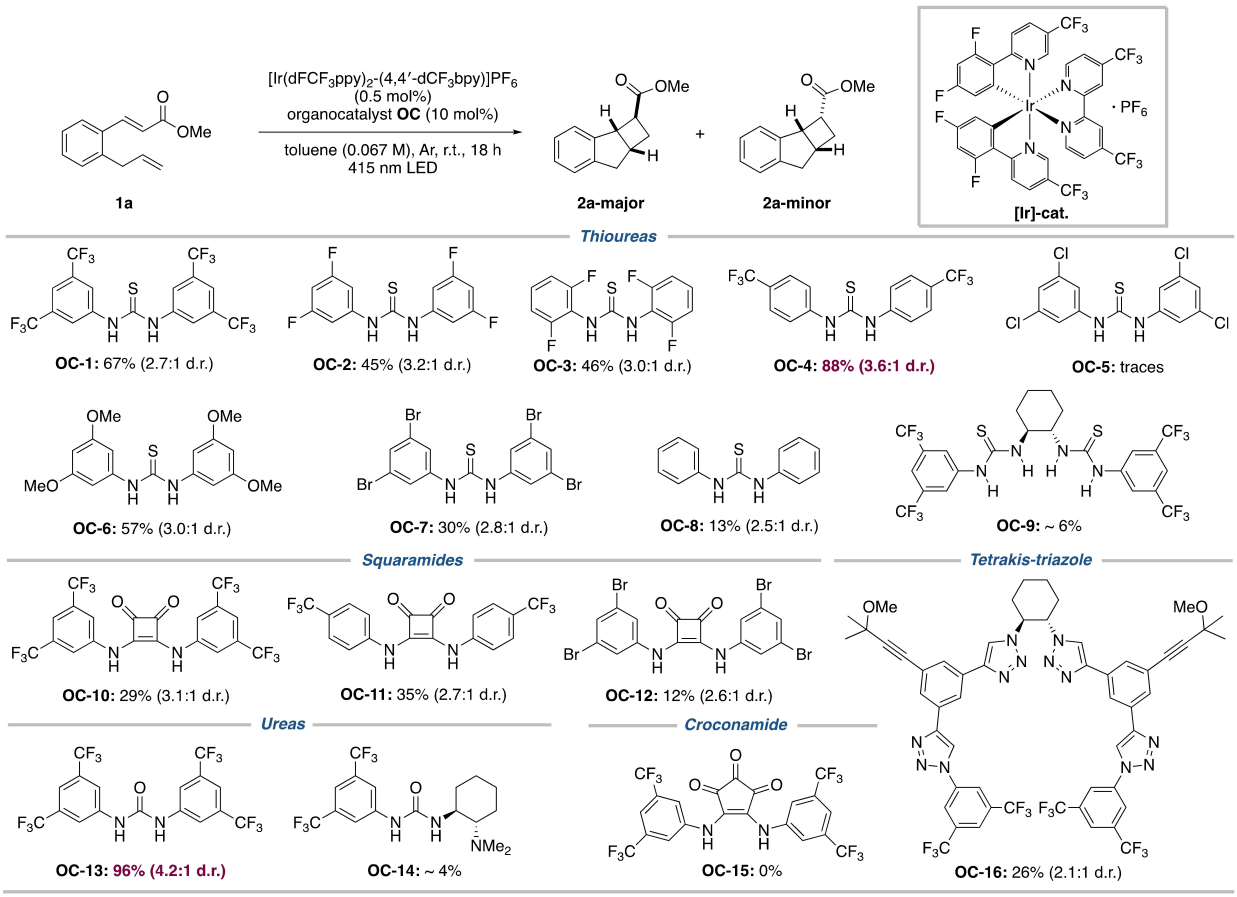
Scheme 2. Preliminary results with and without HB-catalyst. NMR-yields determined using CH_2Br_2 as internal standard.

delight, the desired cyclic product **2 a** could be then obtained in 67% and 71% NMR-yield, respectively.

Encouraged by these results, we next screened a variety of HB-catalysts in toluene as solvent (Scheme 3). Bis-aryl thioureas with different substitution patterns at the aromatic groups (**OC-1–8**) or a bis-thiourea (**OC-9**) were first evaluated. Although a clear trend could not be identified, electron withdrawing groups that lead to stronger HB-donors provided higher yields, in which a 4-CF$_3$-substitution (**OC-4**) built the product **2 a** in an improved 88% yield and 3.6:1 d.r. The urea catalyst **OC-13** showed the best performance, leading to the desired product in an excellent 96% NMR-yield and a 4.2:1 d.r., while squaramides **OC-10–12**, croconamide **OC-15** or a tetrakis-triazole catalyst (**OC-16**) proved less efficiency to promote the [2+2]-cycloaddition.[19]

Having identified urea **OC-13** as HB-donor catalyst of choice, different photocatalysts and solvent media were explored to further optimize the reaction conditions (Table 1). Other EnT catalysts such as [Ir[dF(CF$_3$)ppy]$_2$(dtbpy)]PF$_6$ [Ir2][18] and thioxanthone also promoted the reaction, providing the product in a lower 60% and 51% yield, respectively (entries 2 and 3). Moreover, catalysts more prompt to undergo photoredox processes such as Ru(bpy)$_3^{2+}$, Fukuzumi-acridinium, or Eosin Y were not effective in this reaction, leading to traces or no product formation (entries 4–6). This supports an energy transfer event. Furthermore, the use of a photosensitizer and light irradiation were proved to be a requirement for the reaction to proceed (entries 7 and 8, respectively), while the reduction of the amount of **OC-13** to 5 mol% led to a marked drop on both the yield and diastereoselectivity (63%, 3.2:1 *vs.* 96%, 4.2:1 d.r.; entry 9). Thus, the initially used 10 mol% of the [Ir] catalyst provided the best results, achieving a 77% yield of isolated product (entry 1).

Next, the reaction in solvents with different polarity such as hexafluorobenzene, acetonitrile, acetone, TFE, hexafluoroisopropanol (HFIP) and EtOH was investigated (entries 10–15). In all cases, a beneficial combination of photosensitizer and organocatalyst could be observed, being more dramatic for the fluorinated alcohol TFE (entry 14). Thus, the product



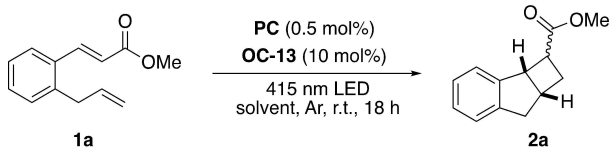
Scheme 3. Screening of HB-donor organocatalysts. NMR-yields determined using CH_2Br_2 as internal standard, and the d.r. by ^{1}H-NMR analysis of the crude reaction.

was formed in 89% yield, whereas no reaction in the absence of the catalyst **OC-13** occurred. However, in EtOH a significant background reaction takes place (entry 13). A trend between the hydrogen bond-donating properties of the alcohol solvent (EtOH (pka 15.9) < TFE (pka 12.4) < HFIP (pka 9.3))[20,21] and the efficiency of the reaction could be observed. Hence, the weaker HB-donor character, the higher yield of the product **2a**. Finally, the use of a higher concentration (0.10 *vs.* 0.067 M) did not significantly affect the conversion to the product (98% *vs.* 96% NMR-yield, entry 16 *vs.* 1), while a further dilution to 0.05 M led to a drop on the yield (83%, entry 17). Therefore, we continue the investigation with 0.067 M.

With the optimized conditions in hand, we then explored the substrate scope and limitations of the co-catalytic system in toluene (Scheme 4).

The reaction of **1a** could be easily upscaled 5-times, providing the same results and allowing the isolation of both isomers (92% combined yield). A variety of alkyl groups on the ester moiety of the substrate were then explored. Branched and bulky alkyl groups such as isopropyl (**2b**), *sec*-butyl (**2c**), cyclohexyl (**2d**) or 1-adamantyl (**2e**) were well-tolerated, delivering the desired cyclobutene products with ~4–5:1 d.r., and the major isomer could be isolated pure in 59–64% yield. Other linear alkyl chains bearing fluorine atoms such as 2-fluoroethyl or perfluorophenylmethyl were then tested, providing the products **2f** and **2g** in similar yields and d.r., except for the benzylic ester in which a slight drop to 3.2:1 d.r. was observed. Furthermore, a chiral ester bearing an additional carbonyl group (ethyl 2-methoxypropanoate) was employed in the reaction. In this case, only traces of the desired product **2h** could be detected by NMR. This suggests a poisoning of the reaction by binding of the HB-donor catalyst to the more accessible ester-unit on the side chain, hindering the activation of the cinnamate group and subsequent EnT event. Subsequently, the substitution tolerance on the allyl moiety was explored by performing the reaction with the derivative **1i** bearing a phenyl substituent. To our delight, the reaction proceeded with high stereocontrol (6.1:1 d.r.) and a good 71% isolated yield. Finally, substitution at the aryl unit of the substrate with electron withdrawing (CF_3) and donating

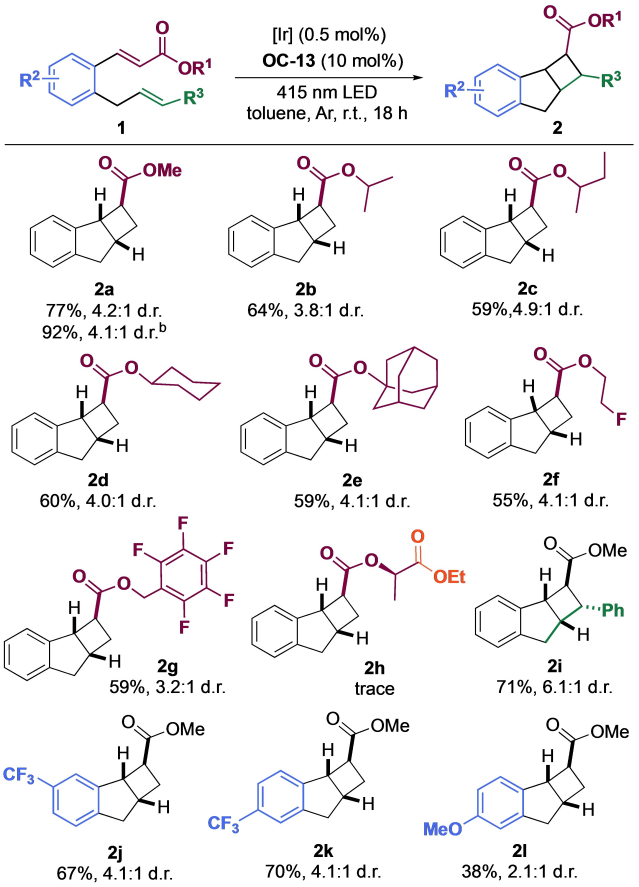
Table 1. Screening of photocatalysts and solvents.[a]



1a 2a

Entry	PC	Solvent	Yield (%)[b]	d.r.[c]
1	[Ir]	toluene	96[77][d]	4.2:1
2	[Ir2]	toluene	60	2.7:1
3	thioxanthone	toluene	51	2.8:1
4	$Ru(bpy)_3(PF_6)_2$[e]	toluene	0	–
5	$Acr^+BF_4^-$[e]	toluene	8	n.d.
6	Eosin Y[f]	toluene	0	–
7	–	toluene	0	–
8	[Ir][g]	toluene	0	–
9	[Ir]	toluene	63[i]	3.2:1
10	[Ir]	C_6F_6	53(28)[h]	4.3:1
11	[Ir]	MeCN	39(13)[h]	3.1:1
12	[Ir]	acetone	62(31)[h]	3.3:1
13	[Ir]	EtOH	56(46)[h]	4.0:1
14	[Ir]	TFE	89(0)[h]	3.3:1
15	[Ir]	HFIP	20(0)[h]	3.0:1
16	[Ir]	toluene[j]	98	2.8:1
17	[Ir]	toluene[k]	83	2.9:1

[a] Conditions: **1a** (0.10 mmol), **PC** (0.5 mol%), **OC-13** (10 mol%) and the corresponding degassed solvent (0.067 M) were placed in a vial under argon and irradiated from the bottom in a photoreactor with a 415 nm LED at r.t. for 18 h.
[b] NMR-yield determined using CH_2Br_2 as internal standard.
[c] d.r. determined by ^{1}H-NMR analysis of the crude reaction.
[d] Isolated yield of the major isomer is given in [ ].
[e] Use of 450 nm LED.
[f] Use of 1 mol% of photocatalyst and 515 nm LED.
[g] No light irradiation.
[h] Yield of reaction in the absence of **OC-13** given in brackets ( ).
[i] Use of 5 mol% of **OC-13**.
[j] Reaction at 0.10 M.
[k] Reaction at 0.05 M. [Ir] = [Ir(dFCF$_3$ppy)$_2$-(4,4′-dCF$_3$bpy)]PF$_6$. [Ir2] = [Ir[dF(CF$_3$)ppy]$_2$(dtbpy)]PF$_6$ (E_T: 61.8 kcal/mol).[18] Acr^+ = 9-mesityl-10-methylacridinium. n.d. = not determined.



Scheme 4. Substrate scope of the reaction. a) The reactions were performed in a 0.1–0.2 mmol scale (see S.I.). Isolated yields of the major diastereoisomer are given. d.r. was determined by ^{1}H-NMR analysis of the crude reaction. b) Results of a 0.5 mmol scale reaction. The sum of isolated yields of major (76%) and minor (16%) isomers is provided.

(OMe) groups was undertaken (**2j**–**2l**). We observed a more efficient reaction with the electron-deficient substrates in terms of both diastereoselectivity and yield (4.1:1 d.r. and up to 70% yield), whereas a methoxy substitution led to the product in a moderate 2.1:1 d.r. and 38% isolated yield of the major isomer.

Mechanistic studies were then carried out. To visualized the proposed interaction and activation of the substrate by hydrogen bonding to the ester moiety, ground-state titration experiments of the HB-donor **OC-13** (host) with increasing amounts of the substrate **1a** (guest) were performed in toluene-d_8 (Figure 1, see S.I. for more details). A clear low-field shift of the hydrogens of the organocatalyst, especially of the NH but also the ortho aromatic C–H groups, could be observed, indicating the expected binding. Furthermore, a notable change in the intensity of the absorption profile when adding the organocatalyst to the substrate was also observed, suggesting a favorable interaction between these species (see S.I., Figure S2).

Regarding the photocatalytic process, quenching (see S.I., Tables S3–S5) and control experiments with another type of EnT sensitizer as thioxanthone (Table 1, entry 3), TEMPO as radical trapping agent and 1,3,5,7-cyclooctatetraene as triplet-state quencher (Scheme 5a), show the expected involvement of an energy transfer rather than a photoredox process. This was also confirmed from the cyclic voltammetry studies, since the reduction potential in the ground state of the substrate **1a** ($E_{1/2}$ = -1.63 V *vs.* SCE; see S.I., Figure S1) does not match with the potential of the photocatalyst in the excited state (E* [Ir*(III)/(IV)] = -0.51 V *vs.* SCE).[18a] Based on this information,

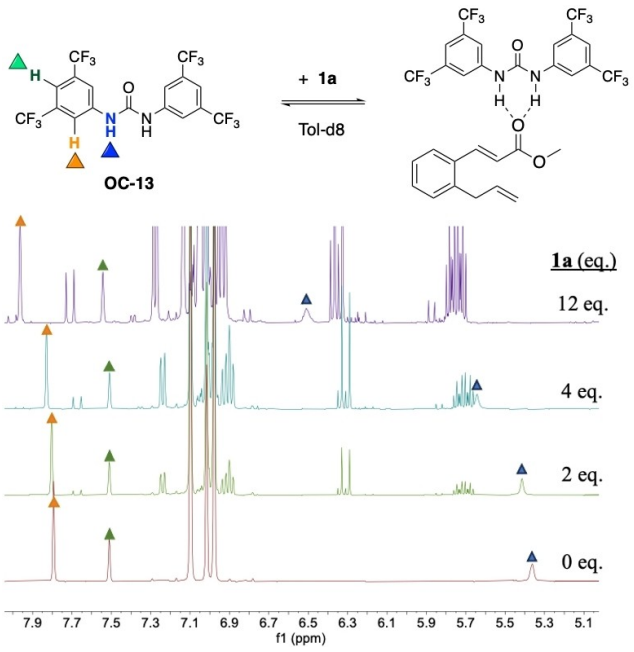
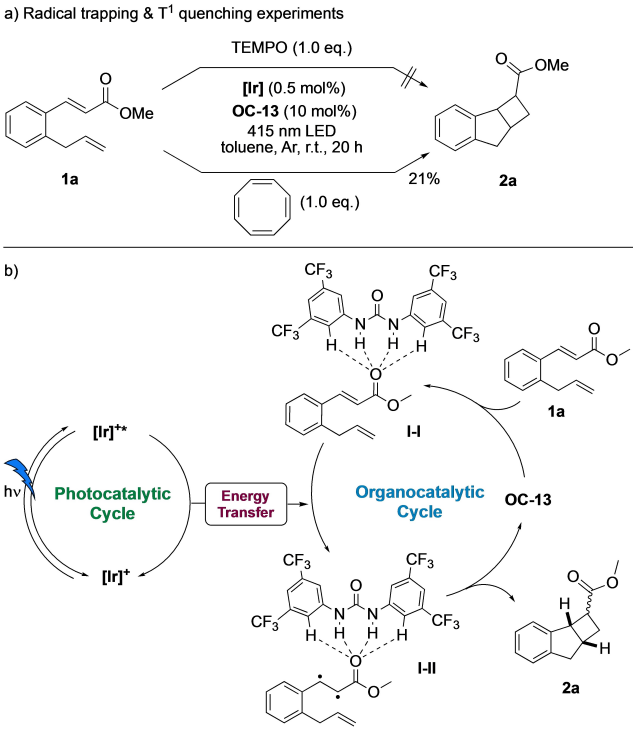


Figure 1. ^{1}H NMR titration of the HB-donor **OC-13** with the standard substrate **1 a** in toluene-d_8 (4 mM) at r.t.



Scheme 5. A) Control experiments, and b) proposed EnT mechanism mediated by HB-activation.

we propose a mechanism (Scheme 5b), in which the substrate is first activated *via* hydrogen bonding by the organocatalyst, forming a complex **I**–**I**. This species is then able to undergo an energy transfer process from the triplet excited iridium photosensitizer to generate a diradical **I–II**. Finally, addition to the allyl group and radical recombination leads to the formation of the four-member ring, followed by product (**2 a**) release and concomitant regeneration of the organocatalyst.

In conclusion, in the present work we have successfully demonstrated the feasibility of a co-catalytic system involving an iridium photocatalyst and a bidentate hydrogen bonding catalyst for the intramolecular [2+2]-cycloaddition reaction of enone-ene. The combination of these two catalysts under optimized conditions allows the access to polycyclic cyclobutanes with good yields and diastereoselectivity. Our mechanistic studies support EnT rather than photoredox pathway. This work not only provides a valuable synthetic strategy for the construction of complex molecules but also highlights further possibilities of hydrogen bonding organocatalysis for the design of novel dual photocatalysis.

Experimental Section

General Procedure for the Photocatalytic [2+2]-Cycloaddition: To a photovial, the corresponding cinnamate ester **1** (0.20 mmol, 1.0 equiv.), the urea-Schreiner catalyst **OC-13** (9.6 mg, 0.02 mmol, 10 mol%) and [Ir(dFCF$_3$ppy)$_2$-(4,4'-dCF$_3$bpy)]PF$_6$ (1.2 mg, 0.001 mmol, 0.5 mol%) were added. The vial was sealed with a metal-cap with septum and flushed with Argon. Under inert atmosphere, degassed toluene (3.0 mL, 0.067 M) was added and the mixture was stirred for 2 min. The photovial was then placed in a photoreactor, irradiated from the bottom with a 415 nm LED and stirred for 18 h at 20 °C. The irradiation was then stopped, and the diastereomeric ratio and NMR-yield were determined by using CH_2Br_2 as internal standard. The product was purified by column chromatography (PE/Et$_2$O 0.5 to 10%).

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