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Effect of Reaction Media on Photosensitized [2+2]-Cycloaddition of Cinnamates

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The outcome of photosensitized [2+2]-cycloaddition reactions of various cinnamates has been compared in different reaction media, including homogeneous organic solutions under inert conditions, degassed water, and aerated physical gels. The reactions were performed under LED blue light ($\lambda_{max}=455$ nm) irradiation and $[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ (1.0 mol%) as photocatalyst. The processes were optimized taking into consideration solvent, gelator, and substrate. Comparative kinetics analyses, as well as the effect of the reaction media on the diastereoselectivity of the process, were evaluated during this investigation. In a number of cases, carrying out the reaction in a less polar solvent, like toluene or highly polar solvent, like water had a tremendous impact on the diastereoselectivity of the process, pointing towards an effect on the stabilization of the putative diradical intermediate in this medium. Moreover, while for reactions run in homogeneous solution oxygen needs to be excluded, no erosion in yield is observed when the photoadditions were run in aerated gel media.

1. Introduction

The bimolecular photocycloaddition reaction[1] have attracted great scientific attention due to its applications in numerous fields such as optical data storage,[2–4] material science,[5–7] cell biology[8–10] and organic synthesis.[11–13] Moreover, stereospecific cyclobutanes are widespread compounds usually found in numerous natural products, insects and microbial species possessing biological activities with potential therapeutic applications.[14–17] Some of the most prominent examples of cinnamic acid and styrene derived dimers include, for instance, truxic acid, piperarborenine D, endiandrin A and magnosalin (*trans*).

In general, several atom economic methods[18,19] have been developed for the synthesis of cyclobutane derivatives. Among those, thermally activated methods[20] have been scarcely reported, while the photochemical pathway utilizing UV light has been known for decades.[21] In contrast, photocatalysis using visible-light was mainly influenced by Yoon and co-workers, who synthesized a wide range of cyclobutanes compounds based on olefins and enones.[22–27] Concurrently with a report by Wu and coworkers,[28,29] some of us have developed an efficient photo mediated intermolecular [2+2]-cycloaddition reaction between simple cinnamates or styrenes based on strong π-π stacking interactions of the aryl groups and a diradical transition state yielding only two diastereomers regioselectively (head-to-head products).[28] Despite the very good yields observed for this dimerization, the diastereoselectivity was found to vary significantly depending on the electronic properties of the aryl group and the steric effects of the ester group of the substrates.

Previous work by Pattabiraman's group on the stereomeric outcome of the dimerization of cinnamates showed that the manipulation of the environment by using non-covalent interactions within macrocyclic cavitands can direct the outcome of the [2+2]-photocycloaddition reaction.[30] A similar approach was published by Ramamurthy and co-workers, where they templated the photodimerization with a water-soluble palladium nanocage[31] or curcubit[8]uril and γ-cyclodextrin.[32] Furthermore, the impact of hydrogel and micellar media on the photodimerization of acenaphthylene has been also studied by Maitra and co-workers.[33] Interestingly, their results showed that the *syn*-to-*anti* ratio was greater in the gel-bound state compared to solution, suggesting that the selectivity apparently is correlated with the rigidity of the gels.

In this work, we hypothesized that a further stabilization of the benzylic radicals' transition state by changing the reaction environment may lead to an improvement of the diastereomeric outcome of the [2+2]-cycloaddition reaction. For this purpose, we designed our study around different solvents for the reaction. The polarity of the solvent system can have a stabilizing effect on the transition state species and to push this concept one step further, also different kinds of low molecular weight gelators were introduced into the system to investigate how they can provide additional interactions aiming to perform the reaction under air without significant losses of yields.

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2. Results and Discussion

Substituted cyclobutanes are accessible *via* photodimerization of cinnamates using visible-light triplet sensitization, which was proposed to proceed through diradical formation[28,29] (Figure 1). The practical importance of this strategy lies on the prevalence of strained cyclobutane structures in a variety of natural products with biological activity.[16] Moreover, a major advantage of photocatalyzed [2+2]-cycloadditions of cinnamates by energy transfer does not depend on the lifetime of the excited state of the photocatalyst, and not on the redox potential of the substrates. In particular, the use of 1.0 mol% of [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 and blue light (λ_{max} = 455 nm; LED_{455}) irradiation under inert gas atmosphere was found to be optimal to achieve a large variety of substituted cyclobutanes in high yields under mild conditions without external additives. Only head-to-head products were obtained with this methodology, which was rationalized by strong π-π stacking of the arene moieties.

The stereoselectivity of the reaction is a consequence of the reversible dimerization of **1** to **A** and its subsequent irreversible collapse to the diastereomers **2** and **3**. If the latter is slowed down, **A** can be populated in its sterically least crowded arrangement which then leads preferentially to the all-*trans* δ-isomer **2**. Thus, the stereoselectivity was found to be dependent on the stabilization of the benzylic radicals: Electron poor substrates were converted to **2** and **3** unselectively, while electron rich ones undergo a slower ring closure and thus allowing an equilibration to the most thermodynamically favored all-*trans* arrangements.[28]

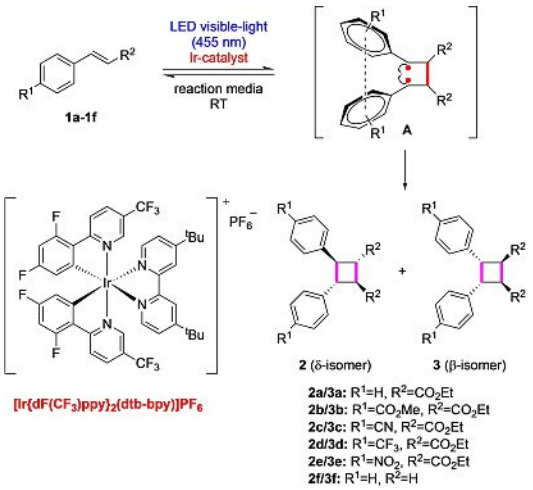


Figure 1. General scheme of visible light mediated [2+2]-cycloaddition reaction in different reaction media studied in this work. Ir-catalyst = [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6.

In order to evaluate the feasibility of this process using supramolecular gels as reaction media, aiming at an improvement of the diastereoselectivity for electron deficient cinnamates **1b–e**, five different LMW gelators **G1**–**G5** were preliminary selected (Figure 2) based on (1) their ability to gel suitable solvents for the [2+2]-cycloaddition reactions (e.g. DMF, toluene, CH_3CN) at different concentrations, (2) the stability of the gels after the incorporation of reactants and catalysts, and (3) their inertness under irradiation conditions. Moreover, the selected gelators offer different modes of self-assembly involving various types of non-covalent interactions (e.g. hydrogen-bonding involving for example amide (**G1**, **G2**), (thio)urea (**G3**, **G5**) and alcohol functions (**G4**), π-π stacking between aromatic rings (**G5**), hydrophobic interactions between long aliphatic chains (**G1**–**G3**, **G5**)), which not only influence the stability of the networks, but they can also interfere with the intermolecular interactions associated to the selectivity observed for the [2+2]-cycloaddition in solution. Thus, diverse self-assembly patterns are expected to influence, at least to some extent, the course of the chemical reactions performed in gel media even when the solvent is the same.

Preliminary comparative experiments were carried out at room temperature (RT) with substrates **1a–b** (in DMF solution (Figure 1 and Table 1, entries 2 and 5) and in gel made of bis-amide glutamic acid-based gelator **G1** (c = 15 g L^{-1}) in DMF (Table 1, entries 1, 4, 5–6). LED blue light (LED_{455}) was used as irradiation source and [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%) as photocatalyst.

The results revealed that the [2+2]-cycloaddition reaction of these cinnamates in gel under aerobic conditions proceeds with significantly higher yields compared to analogous conditions in DMF solution (Table 1, entry 1 vs. 3). Inert conditions

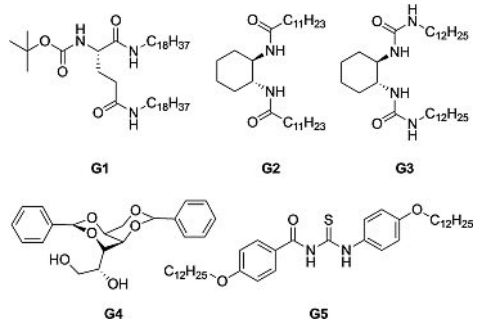


Figure 2. LMW gelators selected for this study: N,N′-bis(octadecyl)-L-Boc-glutamic diamide (**G1**), *N*-((1*R*,2*R*)-2-undecanamidocyclohexyl)undecanamide (**G2**), (+)-(*R*,*R*)-dodecyl-3-[2-(3-dodecyl-ureido)cyclohexyl]urea (**G3**), 1,3:2,4-dibenzylidene-D-sorbitol (**G4**), 4-(dodecyloxy)-*N*-((4-(dodecyloxy)phenyl)carbamothioyl)benzamide (**G5**).

Table 1. Control experiments.[a]

Entry	Substrate	Gelator	Atm.	Conv. [%][b]	Yield [%][c]	d.r. (**2**/**3**)[b]
1	**1a**	**G1**	O_2	100	85	88:12
2	**1a**	–	N_2	100	85	87:13
3[d]	**1a**	–	O_2	–	63	90:100
4	**1b**	**G1**	O_2	100	82	65:35
5	**1b**	–	N_2	100	85	57:43
6[e]	**1a**	**G1**	O_2	0	–	–
7[f]	**1a**	**G1**	O_2	0	–	–

[a] Reaction conditions: Cinnamate (0.5 mmol), photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), dry DMF (1 mL), **G1** (15 g L^{-1}), LED_{455}, 24 h, RT. Abbreviations: Atm. = atmosphere; conv. = conversion; d.r. = diastereomeric ratio (**2** = δ-diastereomer; **3** = β-diastereomer). [b] Determined by ^{1}H NMR analysis of the reaction crude. [c] Isolated yield. [d] Values taken from ref. [28], Table 1, entry 1. [e] Experiment in the absence of catalyst. [f] Experiment in the absence of irradiation.

are required in solution to rival the results obtained in gel (Table 1, entry 1 *vs.* 2; entry 4 *vs.* 5) in terms of regioselectivity, kinetics, conversion and yield. No reaction occurred in the absence of either Ir-catalyst or blue light irradiation (Table 1, entries 6–7).

With these results in hand, we focused our attention on the influence of the gel medium on the diastereomeric ratio by using different LMW gelators (**G1**–**G5**) and cinnamate **1a** (R^1 = H) as model substrate (Table 2). Both the gelator concentration and the solvent were modified in order to optimize the reaction conditions in gel media. The results suggested that both parameters are important and they should be evaluated simultaneously during the optimization experiments of photoredox processes in gel. Thus, a good balance in terms of lower gelation concentration, conversion and diastereoselectivity was obtained with the gel systems increasing the diastereoselectivity from 87:13 in solution to 89:11 (entry 10) in stable gel media. However, from Table 2 it is evident that depending on the parameter of interest there is some flexibility within these conditions.

Furthermore, due to the presence of substrates and catalyst which do not take part of the supramolecular gel network, it should be kept in mind that the minimum gelator concentration suitable for the experiments does not necessarily correspond to the critical gelation concentration (CGC), being defined as the minimum gelator concentration required to form a pure gel in a given solvent. In general, the incorporation of external additives tends to tilt the metastable equilibrium of a supramolecular gel towards the most stable thermodynamic phase (e.g. crystallization, precipitation) over time.[13,15] Such a reduced gel stability could be compensated, at least to a certain extent, by increasing the gelator concentration. The effect of the solvent on the d.r. **2**:**3** was assessed more in detail taking substrate **1a** (R^1 = H) and gelator **G1** as a model system (Table 3). Similarly to solution, different solvents in aerated gel media also affects to some extent the d.r. The lowest diastereoselectivity was found in DMSO (d.r. = 83:17), while toluene and methylene chloride afforded the highest selectivity (d.r. = 91:9). Ratios within this range were found for cyclohexane, acetonitrile, DMF and acetone. It should be emphasized that this behavior is not necessarily extrapolated to other gelators and/or substrates. Overall, these results demonstrate that photoredox reactions in supramolecular gel systems may be modulated by changing the LMW gelator and/or the solvent for a given substrate.

Applying the best reaction conditions found for **1a**, i.e. highest diastereoselectivity for systems in which a stable gel can be formed, we evaluated the outcome of the photodimerization for substrates **1b–1f** in gel media (Table 4), which had given poor selectivities in homogeneous solution.[28] For all substrates the diastereoselectivity could be slightly increased by carrying out the reactions in gel media rather than in the respective solvent alone. In general, the use of gel media has a greater effect in polar solvents like DMF or CH_3CN on the diastereoselectivity than in unpolar solvents (toluene), suggesting a greater stabilization of diradical intermediate **A** in the latter. For all substrates the diastereoselectivity could be increased significantly by carrying out the reactions in a less polar solvent (toluene) compared to previously used DMF, suggesting a greater stabilization of the diradical intermediate **A** in the first.[28] In comparison to that, gel media showed a rather small effect on the diastereomeric outcome of the reaction and tended to have a relatively greater impact in polar solvents like DMF or CH_3CN than in unpolar solvents (toluene).

In agreement with this rational, we found that the reactions proceed efficiently on water, increasing the amount of the *cis*-diastereomer, which is presumably the kinetically preferred one (Table 5). The most dramatic result was obtained with substrates **1b** ($R^1 = CO_2Me$) and **1c** (R^1 = CN), for which the d.r. was inverted in favor to the *cis* product **3** (β-diastereomer) (Table 5, entries 4–5). Moreover, under these conditions the catalyst loading could be efficiently decreased from 1.0 mol% to 0.02 mol% while maintaining the conversion ≥95% (Table 5, entry 3). Surprisingly, although substrate **1e** ($R^1 = NO_2$) was poorly converted on water (11%) even after 72 h (Table 5, entry 7), only the *cis* diastereomer **3** was obtained. In sharp

Table 2. Screening of solvents, gelators and gelator concentrations for the [2+2]-cycloaddition of substrate **1a** (R^1 = H).[a]

Entry	Solvent	Gelator [g L^{-1}]	Conv. [%][b]	d.r. (2/3)[b]
1	DMF	**G1** (15)	100	88:12
2	CH_3CN	**G1** (15)	100	87:13
3[c]	Toluene	**G1** (15)	100	93:7
4	DMF	**G1** (30)	100	88:12
5	DMF	**G2** (15)	100	88:12
6	Toluene	**G2** (15)	46	88:12
7	DMF	**G3** (5)	100	88:12
8	DMF	**G3** (10)	100	87:13
9[d]	Toluene	**G3** (10)	–	–
10	Toluene	**G4** (5)	85	89:11
11[c]	CH_3CN	**G4** (15)	100	86:14
12	Toluene	**G4** (10)	63	89:11
13	Toluene	**G4** (20)	95	89:11
14	CH_3CN	**G5** (15)	96	86:14
15[c]	DMF	**G5** (20)	89	88:12
16[c]	Toluene	**G5** (20)	84	91:9
17[c]	Toluene	**G5** (40)	49	91:9

[a] Reaction conditions: Cinnamate **1a** (0.5 mmol), photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), solvent (1 mL), LED_{455}, 24 h, RT, air. Abbreviations: Conv. = conversion; d.r. = diastereomeric ratio (**2** = δ-diastereomer; **3** = β-diastereomer). [b] [d]Determined by ^{1}H NMR analysis of the reaction crude. [c] Gel melted (unstable) [d] No gel formation.

Table 3. Solvent screening for [2+2]-cycloaddition of **1a** in gel made of **G1**.[a]

Entry	Solvent	Gelator	Conv. [%][b]	d.r. (**2**/**3**)[b]
1	DMSO	**G1** (15)	72	83:17
2	Cyclohexane	**G1** (20)	100	88:12
3	CH_3CN	**G1** (15)	99	89:11
4	DMF	**G1** (15)	100	88:12
5	Acetone	**G1** (15)	100	91:9
6	Toluene	**G1** (20)	100	93:7
7	DCM	**G1** (20)	100	91:9

[a] Reaction conditions: Cinnamate **1a** (0.5 mmol), photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), dry solvent (1 mL), LED_{455}, 24 h, RT, in air. Abbreviations: Conv. = conversion; d.r. = diastereomeric ratio (**2** = δ-diastereomer; **3** = β-diastereomer); DCM = dichloromethane. [b] Determined by ^{1}H NMR analysis of the reaction crude.

Table 4. Substrate screening in solution and in gel media under different conditions.[a]

Entry	Substrate	Solvent	Gelator	Conv. [%][b]	d.r. (**2**/**3**)[b]
1	**1a**	Toluene	–	100	89:11
2	**1b**	DMF	–	100	57:47
3	**1b**	CH_3CN	–	100	68:32
4	**1b**	Toluene	–	100	83:17
5	**1b**	DMF	**G1** (15)	100	65:35
6	**1b**	DMF	**G3** (5)	100	64:36
7[c]	**1b**	Toluene	**G4** (5–20)	–	–
8[d]	**1b**	CH_3CN	**G5** (10)	100	72:28
9	**1c**	DMF	–	100	60:40
10	**1c**	Toluene	–	100	75:25
11	**1c**	DMF	**G1** (15)	100	64:36
12	**1c**	DMF	**G3** (5)	100	64:36
13	**1c**	Toluene	**G4** (5)	100	84:16
14[d]	**1c**	CH_3CN	**G5** (10)	100	72:28
15	**1d**	DMF	–	100	68:32
16	**1d**	Toluene	–	86	79:21
17	**1d**	DMF	**G1** (15)	100	72:28
18	**1d**	DMF	**G3** (5)	100	69:31
19	**1d**	Toluene	**G4** (5)	72	80:20
20[d]	**1d**	CH_3CN	**G5** (10)	100	75:25
21	**1e**	DMF	–	97	54:46
22	**1e**	Toluene	–	92	80:20
23	**1e**	DMF	**G1** (15)	95	56:44
24	**1e**	DMF	**G3** (5)	96	56:44
25	**1e**	Toluene	**G4** (5)	96	81:19
26[d]	**1e**	CH_3CN	**G5** (10)	91	62:38
27	**1f**	DMF	–	23	75:25
28	**1f**	DMF	**G1** (15)	28	76:26
29	**1f**	DMF	**G3** (5)	30	76:24
30	**1f**	Toluene	**G4** (5)	Traces (< 1)	–
31[d]	**1f**	CH_3CN	**G5** (10)	34	68:32

[a] Reaction conditions: Cinnamate (0.5 mmol), photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), solvent (1 mL), LED_{455}, 24 h, RT. Reactions in solution were carried with dry solvents out under strict nitrogen atmosphere, while those performed in gel were performed under aerobic conditions. Abbreviations: Conv. = conversion; d.r. = diastereomeric ratio (**2** = δ-diastereomer; **3** = β-diastereomer). [b] Determined by ^{1}H NMR analysis of the reaction crude. [c] No gel formation. [d] The gelator concentration in this case was reduced to 10 g L^{-1} due to solubility problems compared to substrate **1a** (entry 5).

Table 5. Substrate screening in homogeneous aqueous solution.[a]

Entry	Substrate	Solvent	Conv. [%][b]	d.r. (**2**/**3**)[b]
1[c]	**1a**	H_2O	0	–
2	**1a**	H_2O	99	75:25
3[d]	**1a**	H_2O	95	78:22
4	**1b**	H_2O	100	38:63
5	**1c**	H_2O	94	38:63
6	**1d**	H_2O	95	51:49
7[e]	**1e**	H_2O	11	0:100
8	**1f**	H_2O	100	70:30

[a] Reaction conditions: Cinnamate (0.5 mmol), photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), distilled degassed H_2O (1 mL), LED_{455}, 24 h, RT, nitrogen atmosphere. Abbreviations: Conv. = conversion; d.r. = diastereomeric ratio (**2** = δ-diastereomer; **3** = β-diastereomer). [b] Determined by ^{1}H NMR analysis of the reaction crude. [c] Control experiment in the absence of catalyst. [d] 0.02 mol% catalyst. [e] The same result was obtained after 72 h. Note: Reactions could be scaled up to 1.1 mmol of substrate without detriment in the yield and selectivity.

contrast, the reaction of this substrate in homogeneous DMF solution afforded the corresponding diastereomers **2**:**3** with a d.r. of 57:47.[28]

These results motivated us to test the reaction also in a series of aqueous micellar systems. However, the results indicated no effect of the micelles on the outcome of the reaction (see ESI, Table S1).

Standard kinetics studies using **1a** as model substrate showed second-order reactions in both homogeneous solution and gel media (Figure 3). Reactions in both DMF solution and in gel media made of DMF/**G1**, DMF/**G2**, DMF/**G3** and CH_3CN/**G5** displayed comparable turn over frequencies (TOF) within the range $7–8\times10^{-2}$ min^{-1} and half-life times ($t_{1/2}$) about 6–8 h. Comparing the kinetics parameters with those from the reactions in degassed water, we found a much faster reaction time for the latter with a TOF of 22.9×10^{-2} min^{-1} and a half-life of 2.9 h. In sharp contrast, reactions performed in toluene/**G4** as gel medium were slowed down to TOF and half-life values of of 1.6×10^{-2} min^{-1} and 29.9 h, respectively.

Studies of the thermal stability of the gel systems revealed that those with the highest influence on d.r., i.e. toluene/**G4** and CH_3CN/**G5**, also showed the highest *gel*-to-*sol* transition temperatures (T_{gel}) (i.e. 90 °C and 76 °C, respectively) (Table 6, entries 4–5). In contrast, DMF/**G1**, DMF/**G2** and DMF/**G3** aerated gels, which caused the least impact on d.r., displayed T_{gel} values $\leq$ 64 °C (Table 6, entries 1–3). This apparent correlation is similar to that previously observed for the photodimerization of acenaphthylene in hydrogels.[33]

Table 7 and Figure 4 summarize the influence of the surrounding media (i.e. inert homogeneous solution and aerated gel) on the d.r. and isolated yields of the [2 + 2]-cycloaddition reaction under optimized conditions for each

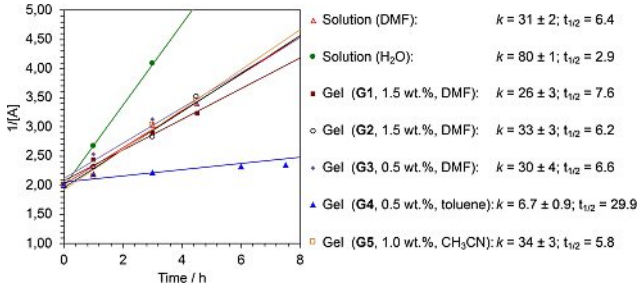
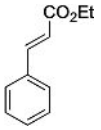
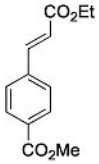
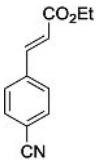
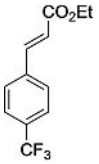
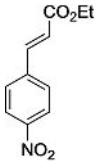
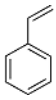


Figure 3. Second order kinetics of the [2 + 2]-cycloaddition model reaction in different reaction media. Reaction conditions: Cinnamate **1a** (0.5 mmol), [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), solvent (DMF, toluene, CH_3CN or H_2O) (1 mL), LED_{455}, RT. Reactions in solution were carried with dry solvents out under strict nitrogen atmosphere, while those performed in gel were performed under aerobic conditions. Rate constants, *k*, are given in ($\times10^{-2}$) M^{-1} h^{-1}; half-lives, $t_{1/2}$, are given in h. Additional kinetics parameters are available from the authors upon request.

Table 6. *Gel*-to-*sol* transition temperature (T_{gel}) of the gels prepared with the different gelators. Concentrations and solvents correspond to those used in the experiments.

Entry	Substrate	Solvent [1 mL]	T_{gel} [°C]
1	**G1** (15)	DMF	50 ± 2
2	**G2** (15)	DMF	60 ± 2
3	**G3** (5)	DMF	64 ± 2
4	**G4** (5)	Toluene	90 ± 2
5	**G5** (10)	CH_3CN	76 ± 2

Table 7. influence of gel media on the diastereomeric ration (d.r.) under optimized conditions.[a]

Substrate	 **1a**	 **1b**	 **1c**	 **1d**	 **1e**	 **1f**
Reaction in homogeneous solution						
d.r.[b]	75:25	38:63	38:63	51:49	–[f]	70:30[g]
(yield)[c] in H_2O	(85%)	(81%)	(80%)	(81%)	–[d]	–[d]
d.r.[b]	87:13	57:47	60:40	68:32	54:46	75:25
(yield)[c] in DMF	(85%)	(85%)	(85%)[e]	–[d]	(86%)[c]	(92%)[c]
d.r.[b] in toluene	89:11	83:17	75:25	79:21	80:20	–
Reaction in gel media						
d.r.[b]	89:11	72:28	84:16	80:20	81:19	76:26
(yield)[c]	(75%)	–[d]	(74%)	(78%)	(75%)	–[d]
[gelator/solvent]	**G4**/toluene	**G5**/CH_3CN	**G4**/toluene	**G4**/toluene	**G4**/toluene	**G1**/DMF

[a] Reaction conditions: Cinnamate (0.5 mmol), photocatalyst [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 (1.0 mol%), solvent (1 mL), LED_{455}, 24–72 h, RT, gelator (i.e. **G1** (15 g L^{-1}), **G4** (5 g L^{-1}), **G5** (10 g L^{-1})). Reactions in solution were carried with dry solvents out under strict nitrogen atmosphere, while those performed in gel were performed under aerobic conditions. Unless otherwise indicated, all conversions determined by ^{1}H NMR analysis of the reaction crude were ≥95%. [b] Diastereomeric ratio (**2** = δ-diastereomer; **3** = β-diastereomer). Determined by ^{1}H NMR analysis of the crude. [c] Isolated yield. [d] Not-isolated. [e] From reference [18]. [f] Diastereomeric ratio not determined. Conversion = 12%. [g] Conversion = 89%.

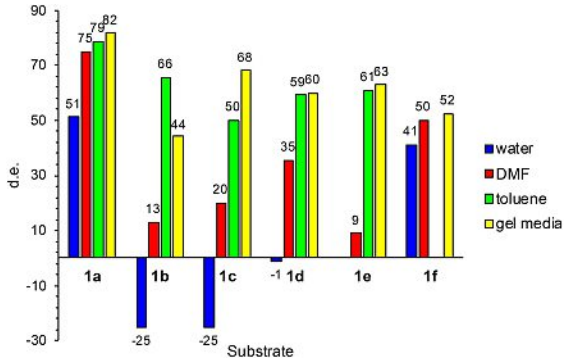


Figure 4. Diastereomeric excess (d.e.) obtained for substrates **1a**–**1f** in different reaction media as described in Table 7.

substrate and reaction medium. The lowest impact was observed on styrene (**1f**) bearing the electron richest double bond, followed by substrate **1a** (R^1 = H), where the increment in diastereomeric excess (d.e.) going from water or DMF solution to less polar solvent toluene or gel is higher than for **1f**. Substrates **1b** (R^1 = CO_2Me), **1c** (R^1 = CN), **1d** (R^1 = CF_3) and **1e** (R^1 = NO_2) having the electron poorest double bonds, showed the highest influence of the surrounding environment, being the mentioned increment of d.e. ca. 6 to 9 times higher compared to **1f**.

Overall, the foregoing results suggest a potential stabilizing effect of less polar environments (toluene, gel media) on the transition state providing more time to equilibrate before ring closure, which results in higher yields of the sterically most favorable *trans* isomer. Finally, it is worth mentioning that the [2 + 2]-cycloaddition could also be scaled up in aerated gel media. For instance, the reaction with 1.0 mmol of substrate 1d (R^1 = CF_3) in toluene/G4 gel in air afforded the desired product in ca. 80% isolated yield and 60% d.e.

3. Conclusions

[2 + 2]-Cycloadditions of cinnamates can be efficiently carried out in solution under LED blue light (λ_{max} = 455 nm) irradiation using 1.0 mol% of [Ir{dF(CF_3)ppy}$_2$(dtb-bpy)]PF_6 as photocatalyst under inert atmosphere. This study demonstrates that such photoredox processes can also be performed under aerobic conditions using supramolecular gels as reaction media instead of standard homogeneous solutions under inert conditions. In general, kinetics parameters in both solution and gel environments are comparable, while the diastereomeric ratio of the *trans* and *cis* diastereomers of the formed substituted cyclobutanes was found to be highly dependent on the polarity of the environment increasing highly from polar solvents (water, DMF) to less polar (toluene, gel media) in favor of the *trans* product. Thus, the reaction media provides some degree of stabilization of the biradical intermediate **A**, slowing down the ring closure step and, hence, facilitating the equilibration towards the sterically most favorable all-*trans* arrangements. A judicious balance between solvent and LMW gelator allows carrying out the reactions without detriment in conversion, kinetics and regioselectivity compared to inert homogeneous solutions, and in most cases even with slight improvement in diastereoselectivity. Furthermore, the [2 + 2]-cycloaddition reaction was also found to proceed on degassed water with much lower catalyst loading (0.02 mol%), albeit with a decrease, and

in some cases inversion, of the diastereoselectivity. As a general trend, polar solvents greatly increase the kinetic of the [2+2]-cycloaddition but also increase the formation of the *cis*-diastereomer **3**. This suggests that the biradical **A** is less stabilized in polar media, since it does not benefit from polar effect. Overall, the results from this study, together with the facile operation of the method with aerated gels, might be relevant for future process automatization, especially for high-throughput screening of potential photocatalysts for similar photoredox reactions.

Experimental Section

Material and Methods

Unless otherwise specified, all reagents, starting materials and solvents (p.a. grade) were purchased from commercial suppliers (i.e. ABCR, Acros, Sigma-Aldrich, TCI or Merck) and used as received without further purification. Cinnamates **1a**, **1e**, **1f** were purchased from Sigma-Aldrich. Synthesis of starting materials requiring oxygen- or moisture-sensitive reagents were carried out using flame-dried glassware, degassed solvents and Schlenk lines. We have previously characterized most reaction products reported in this paper, being the spectroscopic data identical to those reported.[28] For the sake of clarity, ^{1}H NMR data for all known compounds as well as full characterization of new compounds **1d**, **2d** and **3d** are included in this section.

Thin layer chromatography (TLC) analyses were performed using pre-coated TLC-sheets ALUGRAM® Xtra SIL G/UV$_{254}$. Visualization was accomplished with UV light (λ_{max} = 254 nm).

Column chromatography and flash chromatography were performed using silica gel with particle size 63–200 μm and 40–63 μm, respectively, as the stationary phase.

High-resolution mass spectra (HRMS) were obtained according to the IUPAC recommendations (2013) from the central analytic mass spectrometry facilities of the Faculty of Chemistry and Pharmacy at the University of Regensburg.

NMR spectra were recorded with a Bruker Avance 400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz, ^{19}F NMR: 376 MHz) or a Bruker Avance 300 (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz, ^{19}F NMR: 282 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peak ($CHCl_3$, 7.26 ppm). Coupling constants (*J*) are given Hertz (Hz). The following notations are used to indicate the multiplicity of the signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Photochemical reactions were performed using a custom-made set-up[16] with an array of suitable LEDs (3.5 V, 700 mA), i.e. $\lambda_{ex} = 455 \pm 15$ nm, connected to a power supply. The irradiation device was equipped with a stainless-steel jacket to maintain refrigeration of the vials. The distance between the LEDs and the reaction vials was adjusted to 0.9 ± 0.1 cm. The apparatus also allows magnetic stirring of the reaction mixtures. The reported yields are referred to the isolated compounds unless otherwise stated. Oxygen- and moisture-free reactions were carried out with dry and degassed solvents, as well as glassware subjected to several evacuation (vacuum)/refill (nitrogen) cycles.

Gels were prepared in 5 mL snap glass vials having a specific amount of the desired gelator and solvent (p.a. grade). The mixture was gently heated with a heat gun until the solid material was dissolved. The resulting isotropic solution was allowed to cool down to RT affording the corresponding gels. No control over temperature rate during the heating-cooling process was applied. Double-distilled water was purified additionally using a Millipore water-purifying system (Merck) prior usage.

T_{gel} values were determined using a calibrated thermoblock at a heating rate of ca. 5 °C/min.[34] The temperature at which the gel started to break was defined as T_{gel} with an estimated error of ± 2 °C after several heating-cooling cycles. Each measurement was made at least by duplicate and the average value reported.

Synthesis of photocatalyst and gelators

Iridium catalyst, [Ir{dF(CF$_3$)ppy}$_2$(dtb-bpy)]PF$_6$ ((dF(CF3)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtb-bpy = 4,40-di-*tert*-butyl-2,20-dipyridyl), was synthesized according to the procedure described by Reiser and co-workers[35] and the NMR data were in agreement with the literature.[35]

Gelators *N*,*N*′-bis(octadecyl)-L-Boc-glutamic diamide **G1**,[36] *N*-((1*R*,2*R*)-2-undecanamidocyclohexyl)undecanamide **G2**,[37] (+)-(*R*,*R*)-dodecyl-3-[2-(3-dodecyl-ureido)cyclohexyl]urea **G3**,[38] 1,3 : 2,4-dibenzylidene-D-sorbitol **G4**,[39] and 4-(dodecyloxy)-*N*-((4-(dodecyloxy) phenyl)carbamothioyl)benzamide **G5**[40] were synthesized according to literature procedures, being NMR spectroscopic data in agreement with the literature.[36–40]

General Procedure for the Synthesis of Cinnamates

Cinnamates **1b–d** were prepared by means of Horner-Wadsworth-Emmons (HWE) reaction. Typically, potassium *tert*-butoxide (0.84 g, 7.5 mmol, 1.5 equiv) was slowly added to a solution of triethyl phosphonoacetate (1.68 g, 7.5 mmol, 1.5 equiv) in anhydrous THF (50 mL) under a nitrogen atmosphere at 0 °C. The resulting mixture was allowed to stir for 1 h, followed by slow addition of the desired aldehyde (5.0 mmol, 1.0 equiv; i.e. methyl 4-formylbenzoate for **1b**; 4-formylbenzonitrile for **1c**; 4-(trifluoromethyl)benzaldehyde for **1d**) over 5 min. The mixture was stirred for 1 h at 0 °C, and then for 1 h at RT. The progress of the reaction was monitored by TLC analysis. After complete consumption of the starting material, the reaction was quenched by addition of saturated ammonium chloride solution (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the crude reaction mixture was achieved by silica gel column chromatography using hexane/EtOAc solvent mixtures to yield the desired cinnamates (**1b–d**).

Methyl (E)-4-(3-ethoxy-3-oxoprop-1-en-1-yl)benzoate (1b):[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 16.1 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

Ethyl (E)-3-(4-cyanophenyl)acrylate (1c):[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.65–7.59 (m, 4H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

Ethyl (E)-3-(4-(trifluoromethyl)phenyl)acrylate (1d): White solid. Mp 35 ± 1 °C. R_f = 0.34 (19 : 1 hexane : EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.65–7.59 (m, 4H), 6.51 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.44, 142.72, 137.85, 131.72 (q, *J* = 32.7 Hz), 128.17, 125.87 (q, *J* = 3.8 Hz), 120.86, 120.23 (q, *J* = 272.3 Hz), 60.83, 14.30. ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.34. HRMS (ESI$^+$) calculated for $C_{12}H_{11}F_3O_2$ $(M)^+$: 244.0711; Found: 244.0699 $(M)^+$.

General Procedure for the Intermolecular [2+2]-Cycloadditions

An oven-dried 5 mL vial was loaded with [Ir{dF(CF$_3$)ppy}$_2$(dtb-bpy)]PF$_6$ (5 mg, 0.001 mmol), the needed amount of gelator **G1**–**G5** (0.5–1.5 wt.%), solvent (1 mL) and the corresponding substrate (0.5 mmol). The vial was equipped with a rubber septum and the mixture was subjected to ultrasound treatment for 1 min, and then gently heated with a heat gun (heating level 3 out of 10) until a clear solution was obtained. After formation of the gels upon cooling down the mixtures to RT, the vials were placed under 455 nm LED light irradiation for 24 h. After this time, the vials were heated again with a heat gun (heating level 3 out of 10) until complete dissolution of the gel, and 8 drops of the resulting solution were taken for NMR analysis. Brine was added to the crude product mixture (5 mL), and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product was achieved by flash silica gel column chromatography using hexane/EtOAc mixtures affording the desired cinnamates.

Diethyl 3,4-diphenylcyclobutane-1,2-dicarboxylate (2 a/3 a):[28] The titled compound was prepared following the general protocol using 3-phenyl-2-propenoic acid ethyl ester and **G4** (0.5 wt.%) in toluene (1 mL). R_f (**2 a/3 a**) = 0.44/0.33 (9 : 1 hexane : EtOAc).

2 a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.20 (m, 8H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.77 (d, *J* = 9.6 Hz, 2H), 3.46 (d, *J* = 9.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H).

3 a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–6.89 (m, 10H), 4.40 (d, *J* = 6.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.83 (d, *J* = 6.0 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H).

Diethyl 3,4-bis(4-(methoxycarbonyl)phenyl)cyclobutane-1,2-dicarboxylate (2 b/3 b):[28] The titled compound was prepared following the general protocol using 3-phenyl-2-propenoic acid ethyl ester and **G5** (1.0 wt.%) in CH_3CN (1 mL). R_f (**2 b/3 b**): 0.45/0.34 (7 : 3 hexane : EtOAc).

2 b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 4H), 7.35 (d, *J* = 8.3 Hz, 4H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.90 (s, 6H), 3.79 (d, *J* = 9.6 Hz, 2H), 3.48 (d, *J* = 9.5 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H).

3 b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 4H), 6.99 (d, *J* = 8.4 Hz, 4H), 4.47 (d, *J* = 6.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 4H), 3.92 (d, 2H), 3.84 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 6H).

Diethyl 3,4-bis(4-cyanophenyl)cyclobutane-1,2-dicarboxylate (2 c/3 c):[28] The titled compound was prepared following the general protocol using 3-phenyl-2-propenoic acid ethyl ester and **G4** (0.5 wt.%) in toluene (1 mL). R_f (**2 c/3 c**): 0.16/0.8 (4 : 1 hexane : E-EtOAc).

2 c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 4H), 7.38 (d, *J* = 8.3 Hz, 4H), 4.22 (q, *J* = 7.1, 4H), 3.78 (d, *J* = 9.5 Hz, 2H), 3.45 (d, *J* = 9.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H).

3 c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 4H), 7.02 (d, *J* = 8.3 Hz, 4H), 4.48 (d, *J* = 6.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 4H), 3.80 (d, *J* = 5.9 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 6H).

Diethyl 3,4-bis(4-(trifluoromethyl)phenyl)cyclobutane-1,2-dicarboxylate (2 d/3 d): The titled compound was prepared following the general protocol using 3-phenyl-2-propenoic acid ethyl ester and **G4** (1.5 wt.%) in toluene (1 mL). These products were isolated and separated for confirmation. R_f (**2 d/3 d**): 0.29/0.18 (9 : 1 hexane : EtOAc).

2 d: White solid. Mp 78 ± 1 °C. 1H NMR (300 MHz, CDCl3) δ 7.60 (d, *J* = 8.1 Hz, 4H), 7.40 (d, *J* = 8.1 Hz, 4H), 4.22 (q, *J* = 7.0 Hz, 4H), 3.80 (d, *J* = 9.6 Hz, 2H), 3.47 (d, *J* = 9.5 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.01, 144.50, 129.67 (q, *J* = 32.7 Hz), 127.18, 125.77 (q, *J* = 3.8 Hz), 122.25, 77.46, 77.03, 76.61, 61.38, 46.52, 44.60, 14.22. ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.02. HRMS (ESI +) calculated for $C_{24}H_{23}F_6O_4$ $(M+H)^+$: 489.1501; Found: 489.1499 $(M+H)^+$.

3 d: Yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 4H), 7.04 (d, *J* = 8.1 Hz, 4H), 4.49 (d, *J* = 6.3 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 4H), 3.82 (d, *J* = 6.0 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.83, 142.37, 129.17, 128.74, 128.01, 127.25, 127.00, 125.76, 125.20 (q, *J* = 3.7 Hz), 122.16, 61.34, 44.56, 43.35, 14.18. ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.08. HRMS (ESI^+) calculated for $C_{24}H_{23}F_6O_4$ $(M+H)^+$: 489.1501; Found: 489.1501 $(M+H)^+$.

Diethyl 3,4-bis(4-nitrophenyl)cyclobutane-1,2-dicarboxylate (2 e/3 e):[28] The titled compound was prepared following the general protocol using 3-phenyl-2-propenoic acid ethyl ester and **G4** (1.5 wt.%) in toluene (1 mL). R_f (**2 e/3 e**): 0.2/0.16 (10 : 1 hexane : E-EtOAc).

2 e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 4H), 7.46 (d, *J* = 8.8 Hz, 4H), 4.24 (q, *J* = 7.3, 6.9 Hz, 4H), 3.86 (d, *J* = 9.5 Hz, 2H), 3.50 (d, *J* = 9.5 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H).

3 e: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 4H), 7.11 (d, *J* = 8.8 Hz, 4H), 4.57 (d, *J* = 6.1 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 4H), 3.86 (d, *J* = 6.0 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 6H).

1,2-Diphenylcyclobutane (2 f/3 f):[28] The titled compound was prepared following the general protocol using 3-phenyl-2-propenoic acid ethyl ester and **G1** (1.5 wt.%) in DMF (1 mL). Note: Compounds **2 f** and **3 f** are also commercially available. R_f (**2 f/3 f**): 0.43 (19 : 1 hexane : EtOAc).

2 f/3 f: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (m, 7H, *trans*/*cis*), 7.22–7.00 (m, 3H, *trans*/*cis*), 4.11 (m, 2H, *cis*), 3.73–3.61 (m, 2H, *trans*), 2.55 (m, 2H, *trans*/*cis*), 2.47–2.33 (m, 4H, *trans*/*cis*), 2.31–2.16 (m, 4H, *trans*/*cis*).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: [2+2]-cycloadditions · photosensitizers · supramolecular gels · diradicals · diastereoselectivity · photocatalysis

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