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General and Efficient Intermolecular [2+2] Photodimerization of Chalcones and Cinnamic Acid Derivatives in Solution through Visible Light Catalysis

Tao Lei, Chao Zhou, Mao-Yong Huang, Lei-Min Zhao, Bing Yang, Chen Ye, Hongyan Xiao, Qing-Yuan Meng, Vaidhyanathan Ramamurthy, Chen-Ho Tung, and Li-Zhu Wu*

Abstract: Represented by dimerization of chalcones and cinnamic acid derivatives, photo [2+2] cycloaddition is a unique strategy to construct cyclobutanes, the building blocks for a variety of biologically active molecules existing in nature. However, most attempts for the above [2+2] addition focused on solid-state, molten-state or host-guest systems under ultraviolet light irradiation in order to overcome the competition of facile geometric isomerization of nonrigid olefins. Here, we report a general and simple method to realize the intermolecular [2+2] dimerization reaction of these acyclic olefins to construct cyclobutanes in a highly stereo- and diastereoselective manner in solution under visible light, which provides an efficient solution to the long pending problem.

Since the first report of ultraviolet light induced photodimerization of thymoquinone by Liebermann in 1877, photo [2+2] cycloadditions of olefins (*i.e.* Cu(I) catalysis, direct excitation and sensitization, photoredox catalysis) has become a sought after synthetic tool to construct the important building blocks of cyclobutanes from olefins.[1-3] However, geometric isomerization that accompanies bimolecular cycloaddition and low stereo and regio selectivity of cyclobutanes make the intermolecular photo [2+2] cycloaddition of acyclic olefins difficult to be employed as a synthetic tool in solution. Although the first geometric isomerization in solution and cycloaddition of cinnamic acid in solid state was reported in 1881 and 1895, respectively,[4-6] it is rather challenging to acquire a general easily adoptable method for the solution dimerization of cinnamic acids and related acyclic olefins so far. Given the important role of substituted cinnamic acids and chalcones derivatives have historically played in uncovering the hidden secrets of photodimerization of olefins in crystals and organized assemblies,[7-9] we initiated to explore the possibility of the intermolecular [2+2] addition of the nonrigid classical olefins in solution.

To our delight, the intermolecular photo [2+2] cycloaddition and cross photocyclo [2+2] addition of chalcones and cinnamic acids, respectively, occurred efficiently upon visible light irradiation of a catalytic amount of Ir(ppy)$_3$ (*fac*-tris(2-phenylpyridinato-C$_2$,N) iridium) leading to the formation of their cyclobutanes in good to excellent yields. Although the intermolecular [2+2] photodimerization of olefins[10] (for example, cyclic molecules) under visible light (*via* redox process) has been recently highlighted, a general method for the dimerization of classical nonrigid olefins in solution is still missing. In this communication, we highlight the results of our investigations on the visible light induced [2+2] dimerization of several acyclic olefins derived from cinnamic acid and chalcone. The method reported here is fairly general and highly stereo- and diastereoselective. Although intramolecular cycloaddition of acyclic 1,n-dienes is exploited extensively in organic synthesis, as far as we are aware, the intermolecular cycloaddition of acyclic olefins have not received the same level of attention due to the lack of a universal strategy. We believe the current report fulfills the above gap.

The feasibility of the proposed methodology and optimization of the conditions were initially established with chalcone as the substrate and Ir(ppy)$_3$ as the photocatalyst. A degassed 1,4-dioxane solution containing 0.2 mM of olefin and 1 mol % of Ir(ppy)$_3$ was irradiated with blue LEDs (λ = 450 nm) at room temperature. The structure and yield of cyclobutanes obtained in the solution are provided in Table 1. Following results are noteworthy: (a) Parent chalcone, which dimerized inefficiently upon direct excitation by ultraviolet light (0.1 M, $\lambda > 300$ nm, 6% yield), gave major *anti*-head-to-head dimer in 73% yield under the above conditions. (b) Both electron-withdrawing and electron-donating substituted chalcones gave good yields of dimers **3**-**17**. (c) Replacement of phenyl substituent with furan also worked well to afford dimer **13** under the reaction condition. (d) Amongst the chalcones, (*E*)-1-(4-methoxyphenyl)-3-(p-tolyl)prop-2-en-1-one gave the highest yield of the dimer. (e) In addition to chalcone, under the above conditions cinnamic acid derivatives also dimerized with high diastereoselectivities (**18**-**26**, Table 1). (f) Interestingly, even cinnamides showing behaviour similar to chalcones and cinnamates dimerized to main diastereomeric cyclobutanes **27**-**31**. (g) Perusal of Table 1 revealed that in all examples, the cyclobutane products are mainly in an *anti*-head-to-head configuration and the yield of these dimers varied between 38 and 93% that are far higher than in the literature.[7b]

The generality of intermolecular [2+2] photodimerization was established by irradiating two-component systems consisting of 1,1-diphenylethylene with three different olefins, chalcone, cinnamate and cinnamamide. For these experiments, the solvent used was 1,2-dichloroethane, and the concentrations of the two olefins were maintained at 0.2 mM (chalcone or cinnamates or cinnamamide) and 1.0 mM (1,1-diphenylethylene). As illustrated in Table 2, with 1 mol % of Ir(ppy)$_3$ cross [2+2] photodimerization showed good tolerance towards substitution on the carbons of C=O and C=C of the chalcones, cinnamates

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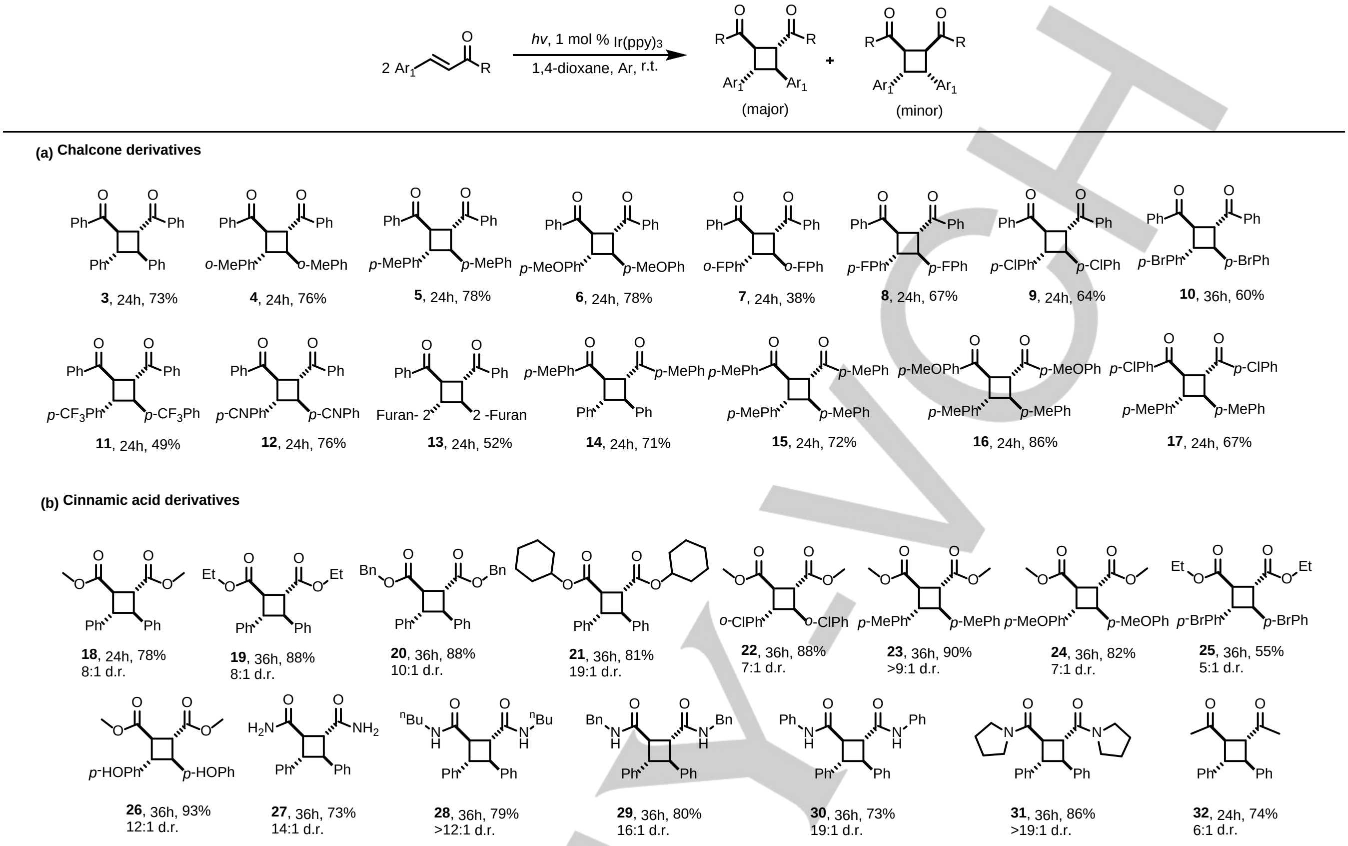
Table 1. Scope of Dimerization Illustrated with Variously Substituted Olefins.[a]



3, 24h, 73%
4, 24h, 76%
5, 24h, 78%
6, 24h, 78%
7, 24h, 38%
8, 24h, 67%
9, 24h, 64%
10, 36h, 60%
11, 24h, 49%
12, 24h, 76%
13, 24h, 52%
14, 24h, 71%
15, 24h, 72%
16, 24h, 86%
17, 24h, 67%
18, 24h, 78% 8:1 d.r.
19, 36h, 88% 8:1 d.r.
20, 36h, 88% 10:1 d.r.
21, 36h, 81% 19:1 d.r.
22, 36h, 88% 7:1 d.r.
23, 36h, 90% >9:1 d.r.
24, 36h, 82% 7:1 d.r.
25, 36h, 55% 5:1 d.r.
26, 36h, 93% 12:1 d.r.
27, 36h, 73% 14:1 d.r.
28, 36h, 79% >12:1 d.r.
29, 36h, 80% 16:1 d.r.
30, 36h, 73% 19:1 d.r.
31, 36h, 86% >19:1 d.r.
32, 24h, 74% 6:1 d.r.

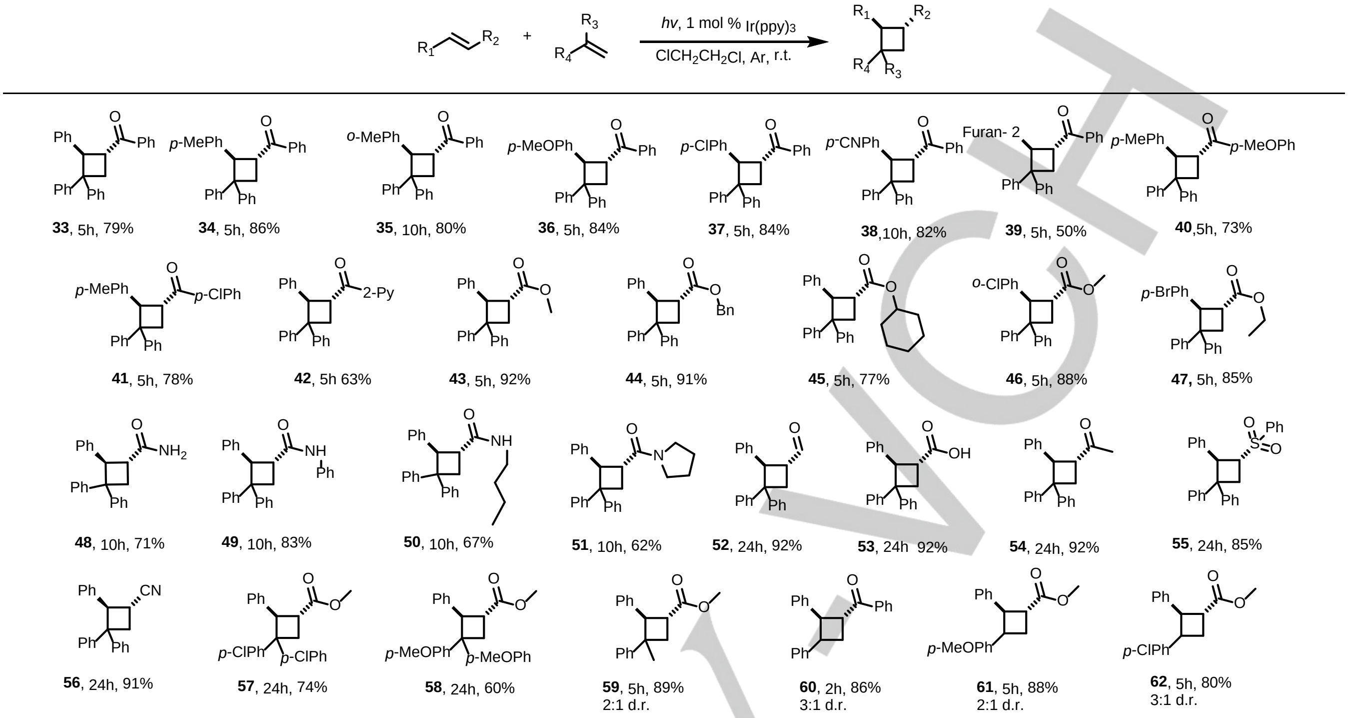
[a] Yield of isolated major product, d.r. (major: minor) determined by ^{1}H NMR analysis of the unpurified reaction mixture. The products of chalcone derivatives had no minor configuration and their byproducts were hardly to be detected or analyzed.

and cinnamamides, yielding cross photodimers with high stereospecificity. Even substrates (refer to the olefin precursors in **52**, **53**, **55**, **56**) that showed low reactivity during homodimerization exhibited high reactivity towards 1,1-diphenylethylene during cross photodimerization. Generality of the cross [2+2] photodimerization was further established with the use of α-methylstyrene and various substituted styrenes as the second olefin (**59**-**62**). From the data presented, it is clear that all obtained cyclobutanes products are in *anti*-configuration.

Control experiments were conducted using chalcone as the model substrate. These experiments established that there was no dimerization without blue light and Ir(ppy)$_3$. As tabulated in Scheme 1, Ir(ppy)$_3$ absorbs up to 500 nm, and has triplet energy of ~58 kcal/mol and photoredox potentials of 0.77 (oxidation) and -1.73 V (reduction) (vs SCE). To probe the value of Ir(ppy)$_3$ and to ascertain whether photoinduced energy or electron transfer is involved in the dimerization process, the reactions were conducted in presence of Ir(ppy)$_2$(dtbbpy)(PF$_6$) and Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)(PF$_6$). These two, having triplet energies similar to Ir(ppy)$_3$, possess reduction potentials lower than Ir(ppy)$_3$. When the solution of chalcone and Ir(ppy)$_2$(dtbbpy)(PF$_6$) or Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)(PF$_6$) was irradiated with blue light, the expected cyclobutane dimers were obtained in moderate yields. Notably, a sharp decreasing yield of dimer to 20% about the template in presence of triethylamine or catalyzed by Ru(bpy)$_3$Cl$_2$ suggested the negative effect of electron transfer on this transformation albeit the reduction potential of the Ir(III) complexes is sufficient to reduce chalcone (Scheme 1). In this situation, we speculated that the Ir(ppy)$_3$-catalyzed intermolecular [2+2] photodimerization proceeds via energy transfer pathway rather than electron transfer one. One would expect isomerization to compete with dimerization because triplet acyclic olefins would lead to isomerization.[11] Indeed, under our irradiation conditions, geometric isomerization competed with dimerization at early stage, but the cyclobutane dimer was the only isolated product at completion of irradiation.

To make sure the feasibility of energy transfer from Ir(ppy)$_3$ to chalcone, we recorded the absorption and emission spectra to determine the singlet and triplet energies of Ir(ppy)$_3$ and chalcone, respectively (see Figure S3). Excitation of Ir(ppy)$_3$ at 450 nm led to strong emission with a maximum at 510 nm in 1,4-dioxane, which is the typical ^{3}MLCT emission of Ir(III) complex.[12] Addition of chalcone to this solution resulted in emission quenching of Ir(ppy)$_3$ at room temperature. Strikingly, when Ir(ppy)$_3$ was excited at 77 K, a new emission with λ_{max} at 590 nm appeared in addition to Ir(ppy)$_3$ emission. The new

Table 2. Scope of Cross [2+2] Reaction Illustrated with Variously Substituted Olefins.[a]



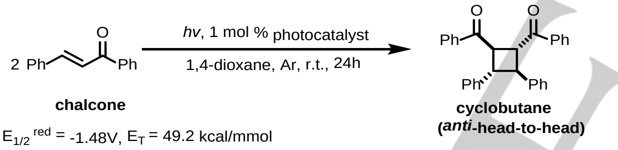
33, 5h, 79% **34**, 5h, 86% **35**, 10h, 80% **36**, 5h, 84% **37**, 5h, 84% **38**,10h, 82% **39**, 5h, 50% **40**,5h, 73%

41, 5h, 78% **42**, 5h 63% **43**, 5h, 92% **44**, 5h, 91% **45**, 5h, 77% **46**, 5h, 88% **47**, 5h, 85%

48, 10h, 71% **49**, 10h, 83% **50**, 10h, 67% **51**, 10h, 62% **52**, 24h, 92% **53**, 24h 92% **54**, 24h, 92% **55**, 24h, 85%

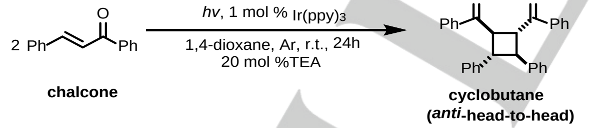
56, 24h, 91% **57**, 24h, 74% **58**, 24h, 60% **59**, 5h, 89% 2:1 d.r. **60**, 2h, 86% 3:1 d.r. **61**, 5h, 88% 2:1 d.r. **62**, 5h, 80% 3:1 d.r.

[a] Yield of isolated product, d.r. (major: minor) determined by ^{1}H NMR analysis of the unpurified reaction mixture.



$E_{1/2}^{red}$ = -1.48V, E_T = 49.2 kcal/mmol

photocatalyst	$E_{1/2}$ (M^+/M^*)	$E_{1/2}$ (M^*/M^-)	E_T(kcal/mmol)	Yield
$Ir(ppy)_3$	-1.73V	+0.31V	57.8	73%
$Ir(ppy)_2(dtbbpy)(PF_6)$	-0.96V	+0.66V	49.2	57%
$Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$	-0.89V	+1.21V	60.8	50%
$Ru(bpy)_3Cl_2$	-0.81V	+0.77V	46.5	20%



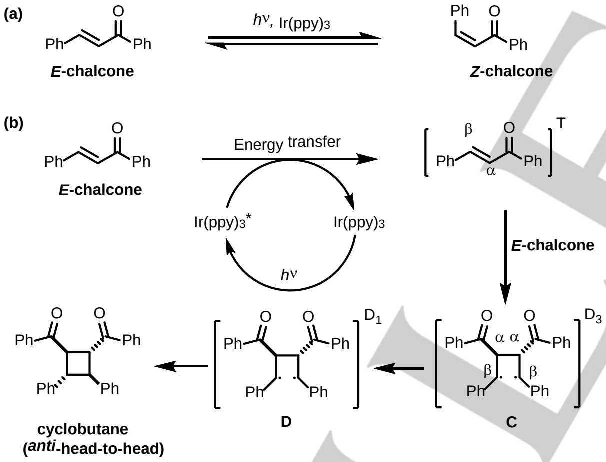
Yield = 21%

Scheme 1. List of Control Experiments Performed (All the Potentials are relative to SCE).

emission was found to have a long lifetime (80 µs) consistent with its assignment to be the triplet of chalcone (see Figure S3). Because of the non-overlapping absorption of chalcone and emission of $Ir(ppy)_3$ at room temperature, the singlet-singlet energy transfer from excited $Ir(ppy)_3$* to chalcone is unlikely. However, the occurrence of overlap between ^{3}MLCT emission of $Ir(ppy)_3$ and phosphorescence of chalcone suggested that the triplet-triplet energy transfer from $Ir(ppy)_3$* to chalcone is likely. The above observations support our contention that in our system $Ir(ppy)_3$ acts as the triplet sensitizer.

As outlined above, the major isomer of products in all cases was found to be *anti*-head-to-head derived from two substrates (Table 1 and Table 2). However, dimerization of unsymmetric olefins in general can give four dimers, *syn*-head-to-head, *anti*-head-to-head, *syn*-head-to-tail and *anti*-head-to-tail. Furthermore, geometric isomerization accompanies the dimerization, thus these dimers could come from two *trans*, a *cis* and a *trans* or two *cis* substrates. To gain an understanding of the high selectivity of *anti*-configuration in our work and the preferred pathway to the cyclobutanes, DFT calculation was performed using the homodimerization of chalcone as the model (for complete details, see Supporting Information). Highlights of the results provided below are consistent with the mechanism proposed in Scheme 2: (a) In the ground state, the *trans*-chalcone is more stable than the *cis*-chalcone while the geometric isomerization is easy in the triplet state. (b) Beginning from the triplet-state complex composed of an excited *trans*-chalcone with a ground state *trans*-chalcone in the *trans*-head-to-head geometry, formation of a diradical intermediate, entrance to the ground state surface through a conical intersection (crossing point) between the triplet and ground state surfaces and closing of the diradical to *anti*-head-to-head dimer are thermodynamically feasible. Importantly, *anti*-head-to-head dimer is slightly more stable than the accretion of two individual olefins. (c) Of the two possibilities of initial bond formation (α-α and β-β in Scheme 2), C–C bond formation between α carbons of the olefins is found to be favourable. This is consistent with the intuitive expectation of formation of a more stable diradical C. (d) The most exciting results relate to the guidance concerning the absence of *syn*-head-to-head dimer. This is because the *syn*-head-to-head dimer is higher in energy than the accretion of two individual olefins. The diradical intermediate formed in this pathway prefers to cleave to two olefins rather than close to form the less stable dimer. (e) Addition of excited *trans*-chalcone to a *cis* one or excited *cis*-chalcone to a *cis* one was found to involve higher energies. Hence, the computational results favour a pathway that involves addition of excited *trans*-chalcone triplet with a ground state *trans*-chalcone to give the stable diradical C (Scheme 2) that closes to yield the isolated *anti*-head-to-head dimer as a sole cyclobutane product.

In conclusion, we report an efficient cost-effective method for the synthesis of highly energy rich and strained cyclobutanes from acyclic C=C bonds. Photophysical studies and DFT calculations revealed that the triplet chalcones and cinnamic acid derivatives produced by energy transfer from the excited Ir(ppy)$_3$* are responsible for the formation of cyclobutanes in highly stereo- and diastereoselective manner, without any extra additives and directing groups in solution. Adopting to visible light catalysis methodology, we have overcome the perennial problem of low yield and low-selectivity of intermolecular [2+2] dimerization of chalcones and cinnamic acid derivatives in solution. Observed results provide confidence that our approach is likely to be general for additional applications.



Scheme 2. Proposed Mechanism.

Acknowledgements

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Keywords: visible light catalysis • [2+2] addition • cyclobutanes • chalcones and cinnamic acid derivatives

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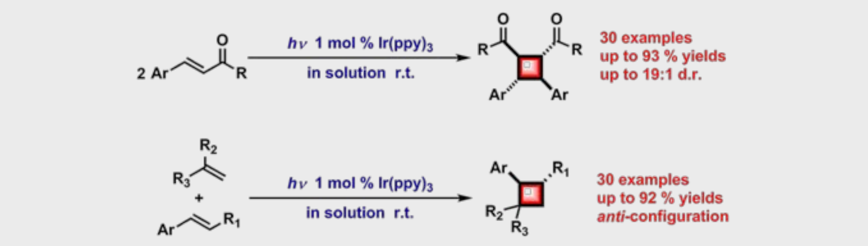

Represented by dimerization of chalcones and cinnamic acid derivatives, we take advantage of visible light induced energy transfer to construct cyclobutanes of nonrigid olefins in a highly stereo- and diastereoselective way in solution, which provides an efficient way toward the long pending issue.

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