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Photosensitised Regioselective [2+2]-Cycloaddition of Cinnamates and related Alkenes

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An efficient method for the synthesis of substituted cyclobutanes from cinnamates, chalcones, and styrenes has been developed utilizing a visible-light triplet sensitisation mode. This reaction provides a diverse range of substituted cyclobutanes in high yields under mild conditions without the need of external additives. Good regioselectivity is obtained due to strong π-π-stacking of arene moieties, whereas diastereoselectivity relies on the electronic effects or *ortho*-substitution of the arene substrate. The utility of this transformation is demonstrated by the formal synthesis of the lignane natural product (±)-Tanegool.

Dimeric and strained cyclobutanes are prevalent structures commonly encountered in natural products. They are found in the plant kingdom, insects, and microbial species, many of which possess a wide range of biological activities with potential therapeutic applications.[1] Cinnamic acid derived dimers, such as truxinic acid, piperarborenine D, or Sagerinic acid derivatives are prominent examples (figure 1).[2] Moreover, styrene-derived naturally occurring cyclobutanes such as Endiandrin A, di-*O*-methylendiandrin A, Magnosalin (*trans*) or Andamanicin (*cis*) are widely used as anti-inflammatory agents, which potently bind to glucocorticoid receptors (GR).[3]

Various synthetic methods have been developed for the synthesis of four-membered carbocycles in an atom economic manner.[4,5] In general, the [2+2]-cycloaddition reaction of alkenes by thermal methods is rare,[6] while photochemical approaches under UV irradiation have long been established.[7] Alternatively, visible-light photocatalysis has emerged for this transformation.[8] In particular, the group of Yoon has developed the visible-light synthesis of a wide range of cyclobutanes derivatives from olefins.[9,10]

Despite the vast developments of photo mediated [2+2] cycloaddition reactions, surprisingly the intermolecular cycloaddition of simple cinnamates or styrenes was so far not achieved efficiently,[11] being summarised in a recent review: *Only if rendered intramolecular and only if the reacting centers are spatially close is a [2+2] photocycloaddition with cinnamates and other β-arylacrylic acid derivatives possible*.[4] Consequently, a number of indirect approaches have been developed for such substrates, requiring additional synthetic steps or additives: Yoon and coworkers have introduced a redox auxiliary for α-β-unsaturated carbonyl compounds, which upon photocycloaddition and subsequent cleavage affords cyclobutane carboxamides, esters, or thioesters.[12] Beeler *et al* described a flow technique for the dimerisation of cinnamates using thiourea derived catalysts in combination with UV-light to afford ester-substituted cyclobutanes.[13]

Very recently, we have demonstrated that α-bromocinnamates can be activated by direct electron transfer[14] or by a dual energy and electron transfer photocascade[15] process.[16] The later is believed to be initiated via a diradical species through energy transfer from the excited photocatalyst, which ultimately collapses to a vinyl radical upon bromine extrusion in the presence of oxygen. In the absence of oxygen, however,

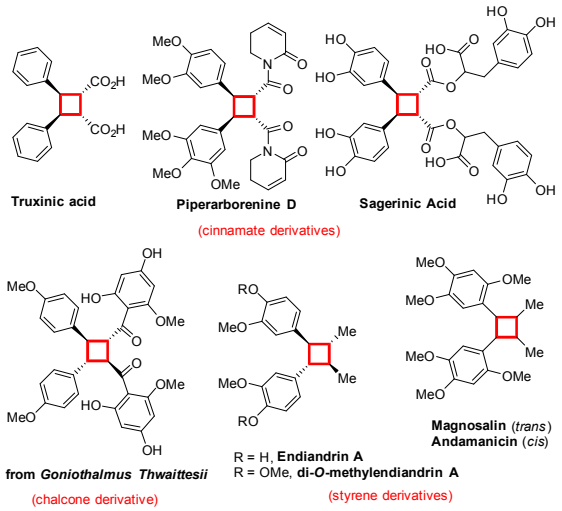

Figure 1 Representative naturally occurring head-to-head cyclobutanes derivatives.

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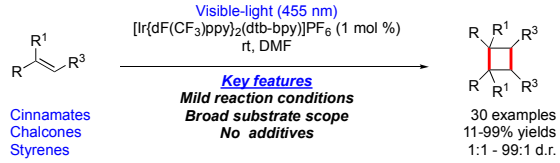
Scheme 1. This work: Visible-light mediated [2+2]-cycloaddtions



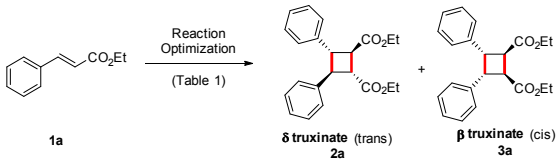
only E/Z-isomerisation was observed, and, in particular, no [2+2]-cycloadducts are formed. Thus, we questioned the utilisation of such diradicals for simple cinnamates, and indeed, we demonstrate here the feasibility of a triplet sensitisation protocol for [2+2]-cycloadditions, which not only allows the synthesis of ester-substituted cyclobutanes but also of those derived from chalcones and styrenes (Scheme 1).

The activation of cinnamates via electron transfer by typical photocatalysts[17] such as $[Ru(bpy)_3]Cl_2$ (bpy = 2,2'-bipyridine, –0.81 V vs SCE)[18] or $[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ ($dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dtb-bpy = 4,4'-di-tert-butyl-2,2'-dipyridyl**, Ir-F**, –0.89 V vs SCE)[19] is thermodynamically unfavourable owing to their high reduction potential (e.g. –1.79 V vs SCE for **1a**).[20] Thus, photoredox catalyzed cycloadditions of these types of unsaturated carbonyl compound is more feasible by energy transfer.[21] The efficiency of energy transfer depends on the excited state lifetime of the photocatalyst, thus it is independent of the redox potentials of the reacting substrates. Having these facts in mind, we initiated our investigation by exploring [2+2]-photocycloaddition of ethyl cinnamate **1a** in the presence of 1 mol % **Ir-F** (τ = 2300 ns[19]) with blue light (LED_{455}) under an oxygen atmosphere (Table 1, entry 1). Gratifyingly, only head-to-head (δ-truxinate, *trans*) **2a** and (β-truxinate, *cis*) **3a** isomers were obtained in a 9:1 ratio and 63% yield. The use of neutral *fac*$[Ir(ppy)_3]$ (τ= 1900 ns, ppy = 2-phenylpyridine, entry 2) and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ (T = 557 ns, ppy = 2-phenylpyridine, entry 3) gave lower yields, while $[Cu(dap)_2Cl]$[22] (τ= 270 ns, dap = 2,9-bis(para-anisyl)-1,10-phenanthroline) and $[Ru(bpy)_3Cl_2]$ (τ = 1100 ns) did not provide any product under the identical conditions (Table 1, entry 4, 5).

The best catalyst (**Ir-F**, Table 1, entry 1) was selected for further optimisation: Pleasingly, the cycloaddition proceeded much more efficiently under inert gas conditions (entry 6), giving rise to **2a**/**3a** (9:1) in 96% yield. Reducing the catalyst amount to 0.5 mol% (entry 7) gave a lower, but still respectable yield (78%). No reaction was observed in the presence of the triplet sensitizer rose Bengal (entry 8), further control experiments suggested the requirement of both, **Ir-F** and visible light (entries 9, 10).

Next, the scope of the reaction was studied (Table 2). Under the optimised conditions, methyl cinnamate (**1b**) provided **2b/3b** in 89% yield and 10:1 d.r., improving on a previous report that yielded the desired cycloadduct in lower yields and selectivity (60%; up to 4:1, Scheme 1a).[13] Likewise, the photodimerisation of β-methyl ethyl cinnamate (**1c**) provides

Table 1 Synthesis of 2a and 3a: Catalyst screening and reaction optimisation[a]



Entry	Photocatalyst (1.0 mol %)	Atmosphere	Yield (%)[b]	d.r. (δ/β)[c]
01	$[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$	O_2	63	9:1
02	*fac*$[Ir(ppy)_3]$	O_2	44	9:1
03	$[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$	O_2	18	9:1
04	$[Cu(dap)_2Cl]$	O_2	traces	-
05	$[Ru(bpy)_3Cl_2]$	O_2	traces	-
06	**$[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$**	**N_2**	**96**	**9:1**
07[d,e]	$[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$	N_2	78	ND[f]
08	Rose bengal, 530 nm	N_2	-	-
09	No catalyst	N_2	NR[g]	-
10	$[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ no light	N_2	NR[g]	-

Reaction conditions: [a] Ethyl cinnamate **1a** (1.0 mmol), photocatalyst (1.0 mol %), dry DMF (2 mL), LED_{455}, 72 h, LED_{455}, room temperature. [b] Isolated yields. [c] Determined by crude ^{1}H-NMR analysis. [d] 0.5 mol % photocatalyst used. [e] Reaction time was 84 h. [f] d.r. not determined. [g] No reaction.

exclusively the δ-diastereomer **2c** in 88% yield. *Para*-substituted cinnamates with donor (+I/+M) or weak acceptor (–I/–M) groups afford the corresponding thermodynamically favored *all-trans* substituted cyclobutanes in good yields and diastereoselectivities (**2d/3d** to **2h/3h,** Table 2). In contrast, strong electron withdrawing substituents decrease the diastereoselectivity to a great extent, presumably due to the destabilisation of the radical species formed as intermediates (see the mechanistic discussion). Substitution in *ortho*-position of the arene dramatically enhances the diastereoselectivity (up to 20:1, Table 2, **2n/3n** to **2p/3p**). Relevant for naturally occurring cyclobutanes (*cf. Fig. 1*), di- or tri-arylsubstituted cinnamates can be employed, providing cyclobutanes **2l/3l** and **2m/3m**. In particular, the isolated δ-isomer (**3l**) has been shown to be a crucial intermediate for the synthesis of lignane natural product (±)-Tanegool.[4,23]

Furan, thiophene, and *N*-Boc-pyrrole substituted cinnamates were also suitable substrates,[4,24] giving rise to desired head-to-head cyclobutanes **2q-s/3q-s** in good yields, however with moderate diastereoselectivity (~1.7:1). Interestingly, for the first two substrates, the unexpected head-to-tail dimers **4q**, **4r** could also be detected in small amounts (see ^{1}H-NMR in the ESI), while in the case of the pyrrole derivative, only the head-to-head dimerisation products **2s/3s** were observed. A limitation of our protocol was encountered for the indole derivative **2t**, which was obtained only in 11% yield (Table 2).

Due to a fast cis/trans isomerisation, thus causing relaxation of the excited state, [2+2] photocycloaddition reactions of chalcones are rare.[25] Nevertheless, we were pleased to see

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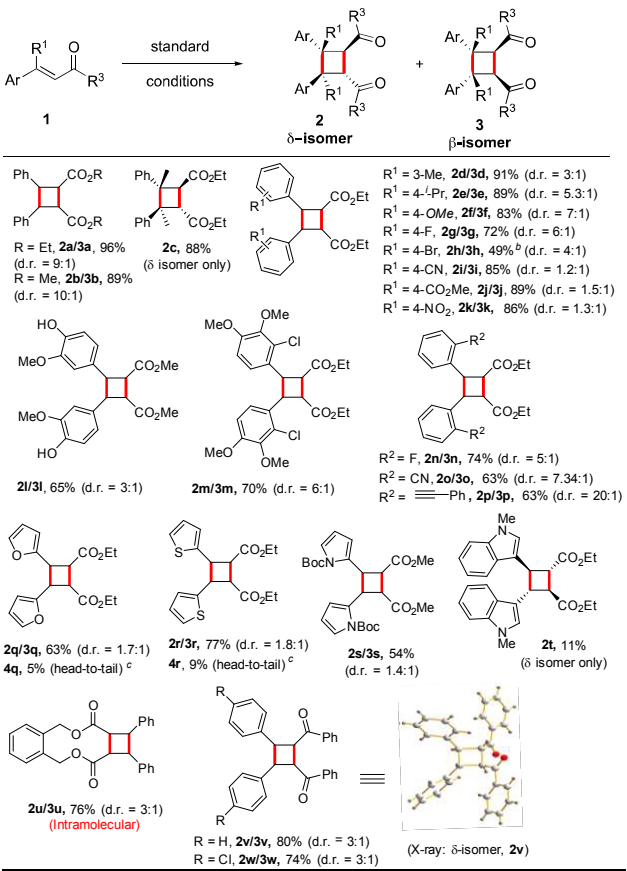
Table 2 Scope for cyclobutanes.[a]



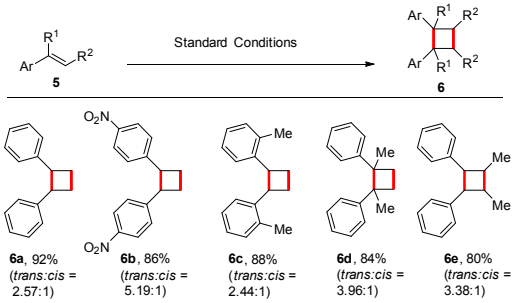
Scope for cyclobutanes: standard conditions: [a] Substrate **1** (1.0 mmol), $[Ir\{dF(CF_3)ppy\}_2(dtb\text{-}bpy)]PF_6$ (1.0 mol %), anhydrous DMF (2 mL), LED_{455}, 72 h, LED_{455}, room temperature, the diastereomeric ratios were determined either by crude ^{1}H-NMR analysis or on the basis of yield of isolated products. [b] Reaction time was 96 h. [c] Head-to-tail products were detected by ^{1}H-NMR analysis.

that chalcones also underwent clean [2+2]-cycloaddition under the photochemical protocol developed, giving rise to the desired cyclobutanes (**2v/3v** and **2w/3w**) in good yields. The δ-isomer of **2v** was unambiguously characterised by single X-ray crystallography. Unfortunately, the attempted cycloaddition of corresponding sulfone, cyano, or nitro substituted alkenes only led to the E/Z-isomerisation of the starting materials.

Next, we explored the intermolecular [2+2] dimerisation of styrenes **5** by energy transfer,[21] given the importance of the resulting cycloadducts for biologically active molecules (*cf.* Figure 1).[3] Intermolecular styrene cycloadditions by photochemical alkene oxidation were reported under visible-light conditions, but require electron rich systems.[10,26] To our delight (Scheme 2), a number of electronically unbiased styrenes **5a,c-e**, but also the electron deficient styrene **5b** provided the corresponding head-to-head cycloadducts **6** in high yields under our conditions.

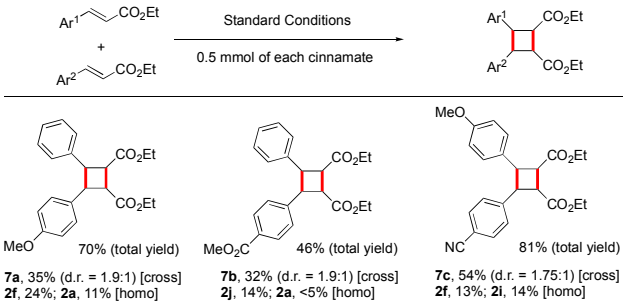
The selective synthesis of unsymmetrical cyclobutanes is challenging and only a few general methods are known.[27] We questioned if two electronically differentiated cinnamates would allow cross coupling under the reaction conditions

Scheme 2: [2+2] cycloaddition of styrenes



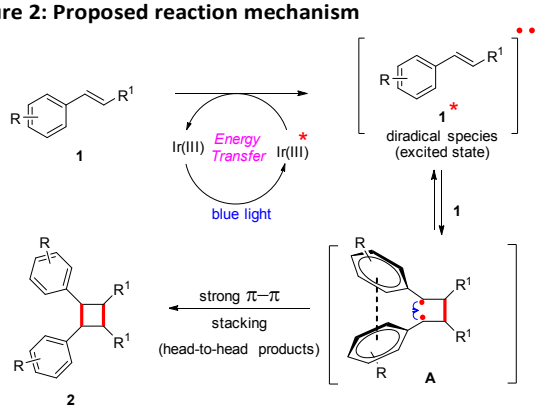
developed. Indeed, in all cases tested (Scheme 3), the desired cross coupled products were obtained and isolated in pure form, however, no appreciable bias beyond the expected statistical distribution towards the cross-coupled dimers was observed.

Scheme 3: [2+2] cross-cycloaddition of cinnamates



Following the rationale put forward by Haag et al for the photodimerisation of cinnamates,[28] we propose that the transformations described here proceed by energy transfer *via* diradical formation (Figure 2).[29]

Figure 2: Proposed reaction mechanism



The photo-excitation of the Ir-catalyst forms the excited Ir*, which transfers energy to the substrate **1** to form the activated diradical species **1***, followed by dimerisation with **1** to give rise to **A**. In agreement with the experimental results, the regioselectivity (head-to-head products) can be rationalized by strong π–π stacking of the arene moieties. The stereoselec-

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tivity is dependent on the stabilisation of the benzylic radicals (Figure 2, **A**), being more effective for electron rich substrates, which consequently undergo slower ring closure to allow equilibrating **A** to the sterically most favourable all-trans arrangements.

In summary, we have developed an effective strategy for the photodimerisation of cinnamates, styrenes, and chalcones which led to the synthesis of substituted cyclobutanes in good to excellent yields with moderate to good diastereoselectivities under mild reaction conditions.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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Table of contents entry:

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