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[2 + 2]-Photodimerization of Stilbazoles Promoted by Oxalic Acid in Suspension

Thanh Binh Nguyen,*[a] Tuan Minh Nguyen,[b] and Pascal Retailleau[a]

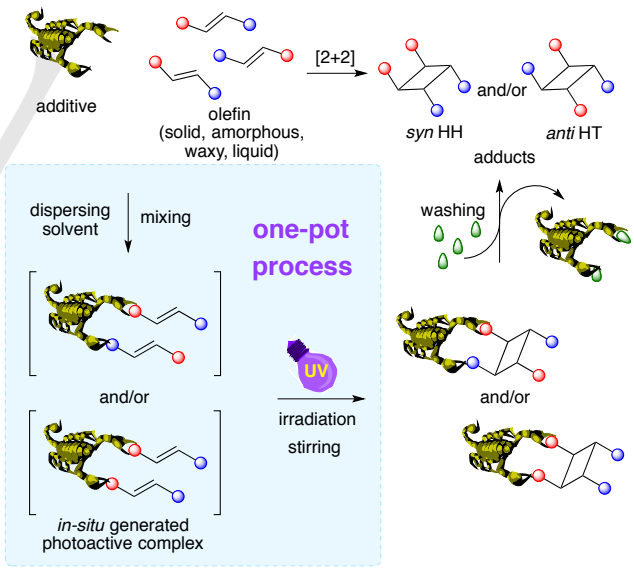
Abstract: In this study we reported on a very simple technique to perform efficiently photodimerization of some vinylpyridines. By irradiating a stirred mixture of several stilbazoles with solid oxalic acid dihydrate dispersed in a non-polar (*e.g.* cyclohexane) or moderately polar (benzene, dichloromethane, dioxane) solvent, the corresponding dimeric cyclobutane adducts were obtained in high yields with excellent of regio- and stereo- selectivities. The strategy could also be applied successfully to oily, waxy or even insoluble stilbazoles. Moreover, the oxalic acid loading could be lowered to sub-stoichiometric amounts. When further optimizations were needed, our strategy was found to be highly flexible to identify other oligocarboxylic acids as alternative additive to improve or even overturn regioselectivity. Oxalic acid and other oligocarboxylic acids were found to be capable of orienting more than fifty stilbazoles toward photodimerization under these conditions.

Photodimerization of olefins to cyclobutane is one of the most studied photochemical transformation. Theoretically, an uncontrolled reaction in solution would lead to a multitude of possible stereoisomers due to the combination of two monomers in *cis* or *trans* configuration in different manners head-head vs head-tail and *syn* vs *anti* addition.[1]

Since the seminal work of Schmidt et al on solid state [2 + 2] photocycloaddition reaction about 50 years ago,[2] different strategies[3] have been developed to achieve such a reaction with reasonable level of reactivity and high stereo- and regio-selectivities, using small organic molecules,[4],[5] metal organic frameworks,[6] coordination with metal cations,[7] cation−π interactions via salt formation,[8] host–guest interactions,[9] and other.[10] All of them were based on the non-covalent rigidification of the relative conformation between two proximal molecules in confined media, especially in crystalline states, to achieve the favorable geometry for the photocycloaddition. Although some important achievements have been made, these strategies are not universal and not practical. Indeed, the screening step to determine the right components for the formation of photoactive complexes with appropriate geometry for subsequent dimerization reaction is time-consuming. This important step is strongly dependent on many factors such as the nature of such components and solvents as well as physical conditions of crystallization. The situation is further complicated for the olefins or additives that exhibit low solubility. Moreover, the structural determination of the obtained complexes and particularly their control of the purity are challenging. Additionally, due to limited molecular motion of starting materials in such rigidified media, full conversion for the [2+2] photodimerization step is not always achieved. All these difficulties explained the fact that most of the reports on photocycloaddition in confined media were performed in small scales with limited number of examples.

In this context, a versatile and flexible screening strategy to determine rapidly the right additives as well as for efficiently performing the photocycloaddition in a very simple manner would be highly desirable, especially for cost-effective and large-scale production of structurally and biologically relevant cycloadducts[11] with well-defined regio- and stereo- chemistry.

In our previous work, we noticed that a mixture of different solid components of similar nature dispersed in an inert solvent could exhibit some degrees of homoselection, i.e. the molecules of exactly the same nature could recognize each other and combine together under irradiation conditions to give the expected correspondent homoadduct in excellent selectivities and yields as if all the homocycloaddition reactions were performed separately.[12]



Scheme 1. Schematic description of our strategy

The cocrystallization between two different components was based on certain specific affinities. Crystalline arrangement of molecules upon exposure to UV irradiation should be considered as a dynamic system with certain degrees of free movement rather than a static structure. With these precedents in mind, we reasoned that such selective and dynamic interactions could take

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place even if the olefin and the additive even in powder states were simply mixed together in an inert solvent (Scheme 1).

Under irradiation conditions, if the resulting cocrystals could achieved the requirement for photodimerization, i.e. were photoactive, the [2+2] photodimerization would be realized under such technically simple one-pot conditions without isolation of photoactive species. Consequently, this strategy would reduce dramatically the necessary time and effort to identify the right additives.

The combination between high dynamicity of solution/suspension state and ordered arrangement of solid state would be an excellent solution to achieve reasonable conversion with excellent regio- and stereo selectivities. Herein, we describe a proof-of-concept demonstrating the feasibility of this idea. As initial point, we set up a model reaction of dimerization of stilbazole **A1** in the presence of a solid additive under 365 nm irradiation.[13]

A range of solid di-, tri-, tetra- and mono- carboxylic acids **a**-**l** was chosen as additives for the possible interaction of their carboxylic acid groups with the nitrogen atom of stilbazole **A1** via hydrogen bond or salt formation (Table 1).

An inert solvent such as cyclohexane was used as a dispersing solvent due to its chemical inertness and very weak interaction with both stilbazole **A1** and carboxylic acid additive. Indeed, all the investigated additives were shown to be practically insoluble in cyclohexane.[14]

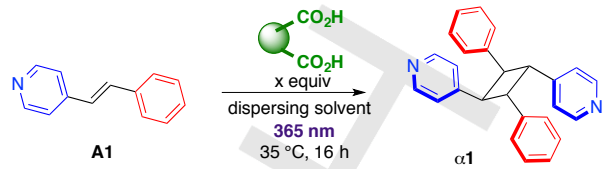
To our delight, while the reaction of **A1** in the absence of additive led to a mixture of the starting materials in both *cis* and *trans* forms in 2:3 ratio (entry 1, Table 1), a relatively clean reaction mixture without any significant degradation of the starting stilbazole was observed when oxalic acid dihydrate was used as an additive in stoichiometric amount (entry 2, Table 1). Most strikingly, with this additive, the truxillic acid type adduct **α1** was formed exclusively and could be isolated in high yield.

Other carboxylic acids such as higher analogues (malonic and succinic acids **b**-**c**, entries 3-4, Table 1), unsaturated acids (maleic and fumaric acids **d**-**e**, entries 5-6, Table 1), benzeneoligocarboxylic acids **f**-**k** (entries 7-12, Table 1) as well as simple monocarboxylic acid such as phenylacetic acid **l** (entry 13) displayed either lower efficiency (leading to lower yields but the reaction mixtures remained rather clean, entries 3, 6-7, 9-10, Table 1) or unsuitability as additive due to the formation of complex mixtures of other isomeric adducts and unidentified side-products (entries 4-5, 8, 11-13, Table 1).

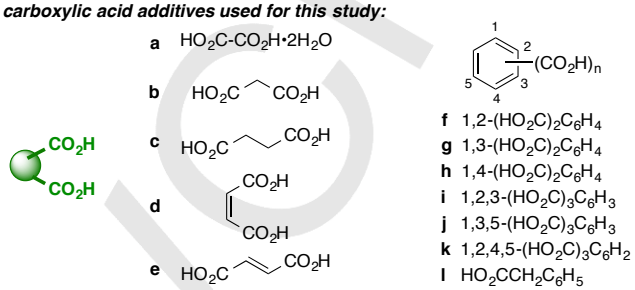
Interestingly, we noticed that a slightly higher yield could be obtained with a slight excess of oxalic acid (entry 14, Table 1), whereas further increasing oxalic acid loading (4 equiv) had a detrimental effect on the yield. Gratifyingly, since a full and clean conversion was achieved in the first case (entry 14, Table 1), adduct **α1** could be obtained by simply removal of oxalic acid with an aqueous $NaHCO_3$ solution. This simplicity is particularly useful for large-scale production of this photoadduct as a single isomer in excellent yield and purity.

Notably, our conditions afforded adduct **α1** in high yields even with catalytic amounts of oxalic acids (entries 16-18, Table 1) although longer reaction times were necessary.

Table 1. Screening of the reaction conditions for olefin **A1**



carboxylic acid additives used for this study:



f 1,2-$(HO_2C)_2C_6H_4$
g 1,3-$(HO_2C)_2C_6H_4$
h 1,4-$(HO_2C)_2C_6H_4$
i 1,2,3-$(HO_2C)_3C_6H_3$
j 1,3,5-$(HO_2C)_3C_6H_3$
k 1,2,4,5-$(HO_2C)_3C_6H_2$
l $HO_2CCH_2C_6H_5$

Entry[a]	Additive (x equiv)	Solvent	Yield of **α1** (%)[b]
1	-	CyH	0[d]
2	**a** (1)	CyH	95
3	**b** (1)	CyH	65
4	**c** (1)	CyH	40
5	**d** (1)	CyH	-[c]
6	**e** (1)	CyH	75
7	**f** (1)	CyH	89
8	**g** (1)	CyH	-[c]
9	**h** (1)	CyH	87
10	**i** (1)	CyH	85
11	**j** (1)	CyH	-[c]
12	**k** (1)	CyH	-[c]
13	**l** (1)	CyH	-[c]
14	a (1.6)	CyH	99 (97[e])
15	**a** (4)	CyH	80
16	**a** (0.5)	CyH	70
17	**a** (0.2)	CyH	85[f]
18	**a** (0.1)	CyH	80[f]
19	**a** (1.6)	PhMe	99[g]
20	**a** (1.6)	$CHCl_3$	99[g]
21	**a** (1.6)	EtOAc	99[g]
22	**a** (1.6)	THF	99[g]
23	**a** (1.6)	dioxane	99[g]
24	**a** (1.6)	MeOH	0[g]

[a] Reaction conditions: **A1** (0.2 mmol), additive, dispersing solvent (2 mL), hν 365 nm, 16 h (unless otherwise noted). [b] Isolated yield. [c] Complex mixture according to ^{1}H NMR of the crude mixture. [d] *cis*-**A1**:**A1** 2:3 ratio determined by ^{1}H NMR. [e] Yield of 1 mmol-scale reaction. [f] Reaction time: 72 h. [g] Conversion into adduct **α1** determined by ^{1}H-NMR.

It should be noted that it was possible that the molar ratios between stilbazole **A1** and oxalic acid did not reflect the real stoichiometry of the photoactive complex since the interaction between stilbazole **A1** (partially soluble in cyclohexane) and oxalic acid (totally insoluble in cyclohexane) is not as effective as

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in case where both of these components were freely soluble. Compared to classical template strategy which requires inevitably the use of stoichiometric amount of the template molecules, this result showed clearly high dynamicity of the suspension conditions. This observation is a starting point for further development of catalytic system (similar to solution chemistry) taking advantage of highly ordered molecular arrangement of solid state chemistry.

The same efficiency (yield, regio- and stereo- selectivities) was maintained when using non-polar (hexane, heptane, cyclohexane) or moderately polar (PhH, PhMe, CH_2Cl_2, $CHCl_3$, ethyl acetate, tetrahydrofuran or dioxane) solvents (some examples were shown in entries 19-23, Table 1). In all these cases, the complexes between **A1** and oxalic acid were insoluble in dispersing solvents and both regio- and stereo- selectivities reaction could be considered to be governed by solid state arrangement of the two components.

As expected, when the reaction was performed in a protic solvent such as methanol which could break easily hydrogen bond interaction between **A1** and oxalic acid, the required orientation for successful [2+2]-photodimerization could not be achieved and the corresponding adduct could not be formed (entry 24, Table 1).

With this set of optimized conditions in hand (entry 14, Table 1), we next evaluated the reactivity of a range of stilbazoles **A2-A35** bearing a 4-pyridyl moiety listed in Table 2. In general, most of the tested olefins led to the desired products in excellent yields as a single regio- and stereo- isomers in the presence of an equimolar amount of oxalic acid additive.

It is important to note that for each olefin, a comparative background reaction was performed in the absence of oxalic acid and in the overwhelming majority of cases led to complex mixtures of *cis* and *trans* olefins, α-truxillic and β-truxinic type isomers and other stereo- isomers as well as degradation products in various proportion.

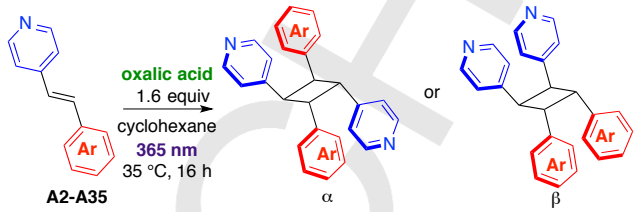
The configuration of [2+2] adducts was determined based on ^{1}H NMR signal of cyclobutane protons (*J* coupling constant and form of these signals). Interestingly, after UV irradiation, most of the tested stilbazoles **A** with different functional groups underwent [2+2] cycloaddition leading exclusively to either α-truxillic acid type adduct (*anti* HT) or β-truxinic type adduct (*syn* HH).

Monoalkylated stilbazoles **A2**-**A5** reacted in the same manner as **A1** and led to the corresponding α-truxinic acid type adducts **α2**-**α5** (entries 1-4, Table 2). On the other hand, 4-isopropyl derivative **A6** formed uniquely **β6** adduct in high yield (entry 5, Table 2).

The photocycloaddition of sterically hindered (*E*)-4-(2,4,6-trimethylstyryl)pyridine **A7** could be achieved in excellent yield of a **α7** adduct although longer reaction time was required (entry 6). Halogenated 4-stilbazoles **A8**-**A16** could provide the corresponding [2+2] adducts also in excellent yields, even for polyhalogenated derivatives of the same or different halogen atoms (entries 7-15, Table 2). All tested halogeno stilbazoles led only to either α or β adduct.

For cyanated 4-stilbazoles, we noticed that the corresponding adduct of *p*-cyano-4-stilbazole **A17** could be formed in excellent yield without any added additive (entry 16, Table 2).[15] Furthermore, the [2+2] photodimerization of *o*-cyano isomer **A18** required oxalic acid additive with inversion of regiochemistry (entry, Table 2).

Table 2. Reactions of β-(4-pyridyl)styrenes **A2-A35**



Entry[a]	A	Ar	T (h)	yield (%)
1	**A2**	4-MeC_6H_4	16	**α2**, 90
2	**A3**	3-MeC_6H_4	16	**α3**, 92
3	**A4**	2-MeC_6H_4	16	**α4**, 95
4	**A5**	4-EtC_6H_4	16	**α5**, 96
5	**A6**	4-*i*PrC_6H_4	40	**β6**, 72
6	**A7**	2,4,6-$Me_3C_6H_2$	72	**α7**, 90
7	**A8**	4-FC_6H_4	16	**α8**, 90
8	**A9**	2-FC_6H_4	16	**α9**, 95
9	**A10**	4-ClC_6H_4	16	**α10**, 95
10	**A11**	2-ClC_6H_4	16	**β11**, 70
11	**A12**	4-BrC_6H_4	16	**α12**, 90
12	**A13**	2-BrC_6H_4	16	**β13**, 94
13	**A14**	2,4-$Cl_2C_6H_3$	16	**β14**, 96
14	**A15**	4-Br-3-FC_6H_3	16	**α15**, 95
15	**A16**	2,4,6-$F_3C_6H_2$	72	**β16**, 70
16	**A17**	4-NCC_6H_4	16	**α17**, 100[b]
17	**A18**	2-NCC_6H_4	16	**β18**, 92
18	**A19**	4-$O_2NC_6H_4$	72	**α19**, 70
19	**A20**	4-$F_3CC_6H_4$	16	**α21**, 94
20	**A21**	4-$HO_2CC_6H_4$	16	**β21**, 87
21	**A22**	4-$MeOC_6H_4$	16	**α22**, 73
22	**A23**	3-$MeOC_6H_4$	72	**α23**, 50
23	**A24**	2-$MeOC_6H_4$	16	**α24**, 95
24	**A25**	2,4,6-$(MeO)_3C_6H_2$	72	**α25**, 55
25	**A26**	4-$AcOC_6H_4$	72	**α26**, 84
26	**A27**	4-$EtCO_2C_6H_4$	16	**α27**, 99
27	**A28**	4-*n*Pr$CO_2C_6H_4$	16	**α28**, 94
28	**A29**	4-*i*Pr$CO_2C_6H_4$	16	**α29**, 92
29	**A30**	1-naphthyl	60	**α30**, 71
30	**A31**	2-naphthyl	60	**α31**, 61
31	**A32**	2-thienyl	16	**α32**, 64
32	**A33**	3-thienyl	16	**α33**, 91
33	**A34**	2-furyl	72	**α34**, 44
34	**A35**	3-furyl	72	**α35**,58

[a] Reaction conditions: **A** (0.2 mmol), oxalic acid dihydrate (40 mg, 0.32 mmol), cyclohexane (2 mL), hν 365 nm, 16-72 h.[b] Yield of the background reaction.

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Other 4-stilbazoles bearing a range of electron withdrawing group (NO_2, CF_3, CO_2H, entries 18-20, Table 2) or electron donating group (MeO, AlkylCO_2, entries 21-28, Table 2) in different positions of the phenyl ring could provide the expected adducts in excellent yield and selectivities.

Amazingly, although stilbazole **A21** bearing a free carboxylic group exhibits very low solubility in most common solvent for crystallization, its photocycloaddition performed with suspended oxalic acid could provide adduct **β21** as the single product in good yield (entry 20, Table 2). The same product was previously obtained indirectly via saponification of the corresponding methyl ester.[4o]

All three regiomeric monomethoxy stilbazoles (**A22**-**A24**) gave the same results in both reactivity and selectivities (entries 21-23, Table 2). The reaction of 2,4,6-trimethoxy stilbazole **A25** proceeded slowly with reasonable yield obtained only after 72 h of irradiation (entry 24, Table 2). The behavior of all four *p*-acyloxy stilbazoles **A26**-**A29** was found to be independent of the acyl chain length and ramification as all of them led efficiently to the expected single products of α-truxinic type stereochemistry irradiation (entries 25-28, Table 2).

The same stereochemistry outcome was obtained with both 1- and 2-naphthyl derivatives (**A30**, **A31**, entries 29-30, Table 2), both thienyl (**A32**-**A33**, entries 30-31, Table 2) and furyl analogues (**A34**-**A35**, entries 31-32, Table 2). We noticed that the reaction of 1-naphthyl derivative should be performed under an inert atmosphere to avoid a side reaction of oxidative cyclization leading to naphtho[1,2-*H*]isoquinoline (entry 29, Table 2).[16] Despite the apparent structural similarity between thienyl and furyl derivatives, the photodimerization of both sulfurated olefins (entries 31-32, Table 2) was found to proceed much efficiently with shorter reaction times and provided the corresponding adducts in higher yields than that of the corresponding oxygenated analogues (entries 33-34, Table 2).

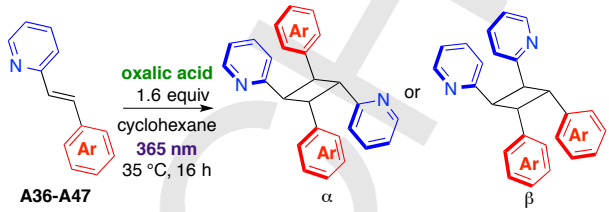
Subsequently, the ability of oxalic acid in promoting selective photocycloaddition was evaluated with 2-stilbazole **A36** and its derivatives (**A37**-**A47**), which were readily available by the condensation of the corresponding benzaldehydes with 2-picoline in the presence of acetic anhydride (Table 3). Such a systematic study on a range of 2-stilbazoles has never been carried out, possibly due to all the difficulties in obtaining well-defined and photoactive cocrystals between this kind of olefins and a suitable template molecule.

As in the previous cases with 4-stilbazoles (Table 2), excellent results were achieved for all 2-stilbazoles listed in Table 3. The reaction worked with a wide range of substituents, including alkyl (entry 2, Table 3), halogen (entries 3-8, Table 3), electron donating groups (methoxy and acyloxy, entry 9, Table 3), and electron withdrawing group (ester, carboxylic acid and nitro, entries 11-12, Table 3). As in the previous case with 4-stilbazole carboxylic acid **A21** (Table 2, entry 20, Table 3), even though **A46** was shown to be slightly soluble in most of the common solvents for cocrystallization and thus unsuitable for the template strategy, its good reactivity showcased an extremely useful complementary aspect of the present strategy.

In an interesting way, simply changing the free carboxylic acid of stilbazole **A46** by its methyl ester **A45** overturned the regiochemistry (entry 10 *vs* entry 11, Table 3).

Oxalic acid additive showed also its high performance in case of 2,4'-diazastilbene **A48**, leading to adduct β**48** (entry 13, Table 3).

Table 3. Reactions of β-(2-pyridyl)styrenes **A36-A47**



Entry[a]	A	Ar	T (h)	yield (%)
1	**A36**	C_6H_5	16	**α36**, 94
2	**A37**	4-MeC_6H_4	16	**α37**, 95
3	**A38**	4-FC_6H_4	16	**α38**, 93
4	**A39**	4-ClC_6H_4	16	**α39**, 93
5	**A40**	3-ClC_6H_4	16	**α40**, 95
6	**A41**	2-ClC_6H_4	16	**α41**, 88
7	**A42**	2,4-$Cl_2C_6H_3$	16	**β42**[b], 90
8	**A43**	4-Br-3-FC_6H_3	16	**β43**, 94
9	**A44**	4-AcO-3-MeOC_6H_3	16	**α44**, 80
10	**A45**	4-MeO_2CC_6H_4	16	**α45**, 90
11	**A46**	4-HO_2CC_6H_4	16	**β46**, 82
12	**A47**	3-O_2NC_6H_4	72	**β47**, 69
13	**A48**	4-Pyridyl	16	**β48**, 72

[a] Reaction conditions: **A** (0.2 mmol), oxalic acid dihydrate (40 mg, 0.32 mmol), cyclohexane (2 mL), hν 365 nm, 16-72 h. [b] **β42**:**α42** 7:1.

Additionally, our strategy also enables the use of some selected stilbazoles **A49**-**A51** bearing a methyl group in the pyridine ring (entries 1-3, Table 4). As in the two previous cases with 2,4-dichlorostilbazoles bearing 4- or 2- pyridyl substituents (**A14** and **A42**) which led to β truxinic acid type adducts β**14** and β**42**, we noticed the same tendency for stilbazole **A51**.

We emphasized that in some cases, the starting stilbazole exists as either an oily liquid, semi liquid, solid with near rt melting point or waxy/amorphous solid. Typically, a solid powder was formed when these stilbazoles were stirred with solid oxalic acid suspended in cyclohexane.

Although most of the above-mentioned results with oxalic acid as the additive were positive, we recognized quickly that some stilbazoles led to the products as a mixture of both α-truxinic and β-truxillic type adducts with low selectivity or were totally photoinactive with this additive. In such difficult cases, the versatility and flexibility of our strategy were demonstrated clearly by simply fine-tuning or reconsidering the choice of additive. For this purpose, we presented some troubleshooting examples.

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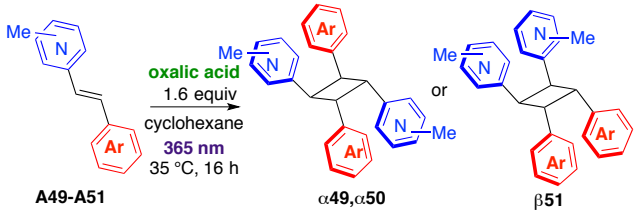
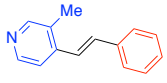
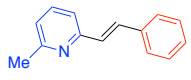
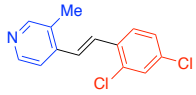
First, when the reaction of 3-pyridyl/2-pyridyl analogue using oxalic acid led to a mixture of both isomers α or β in low regioselectivity (**β52**:**α52** 2.5:1) despite high reactivity. An additional screening of other additives was therefore carried out to improve this low regioselectivity (Scheme 2).

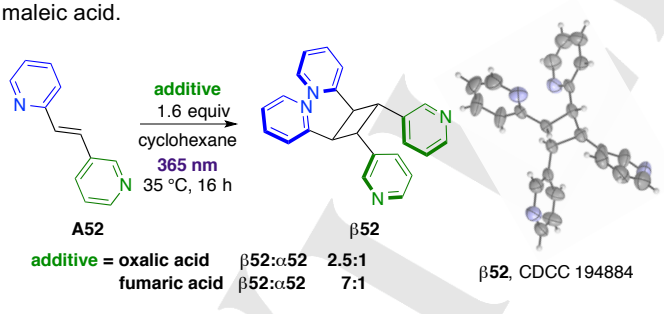
Table 4. Reactions of stilbazoles **A49-A51**



Entry[a]	Stilbazole	T (h)	Product, %
1	 A49	72	**α49**, 72
2	 A50	72	**α50**, 62
3	 A51	16	**β51**, 89

[a] Reaction conditions: **A** (0.2 mmol), oxalic acid dihydrate (40 mg, 0.32 mmol), cyclohexane (2 mL), hν 365 nm, 16-72 h.

The result of such a rapid improvement led to the identification of fumaric acid as a more suitable additive with comparable activity and leading to better regioselectivity **β52**:**α52** 7:1. On the other hand, low reactivity was observed with malonic acid and maleic acid.



Scheme 2. [2+2] Photocycloaddition of **A52**

Second, when the condition using oxalic acid as an additive failed to provide the expected adduct as in the case of *p*-nitro-2-stilbazole **A53** or 2',4'-dinitro-2-stilbazole **A54** wherein the starting material remained unchanged, a screening of new additives found again fumaric acid as an excellent additive to provide exclusively the adducts **β53** and **α54** in good yields (Table 5, entries 1-2). The structure of **β53** was confirmed by X-ray crystallography (Figure 1).

Third, our strategy could be applied successfully to both methyl and ethyl (*E*)-3-(pyridin-3-yl)acrylates **A55**-**A56**, which are semi solid (methyl ester) or liquid (ethyl ester) at rt (Table 5, entries 3-4). For both esters, 1,3,5-benzenetricarboxylic acid **j** was found to be the most suitable additive in terms of both reactivity and selectivities, providing the single adduct **β55**- **β56** in reasonable yields.

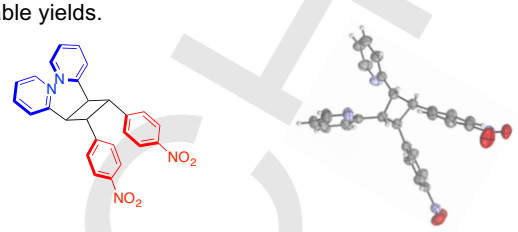
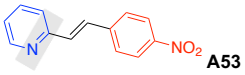
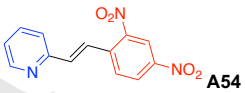
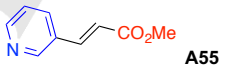
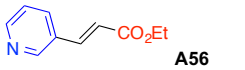


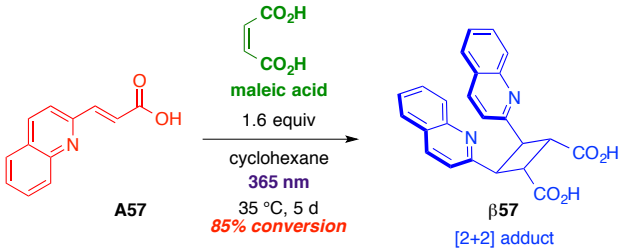
Figure 1. X-ray structure of β53, CDCC 1948883

Table 5. Reactions of olefins **A52-A55**

Entry[a]	Olefin	Additive	T (day)	Yield (%)
1	 A53	**e**	7	**β53**, 55
2	 A54	**e**	7	**α54**, 59
3	 A55	**j**	4	**β55**, 52
4	 A56	**j**	4	**β56**. 51

[a] Reaction conditions: **A** (0.2 mmol), additive **e** or **j** (0.32 mmol), cyclohexane (2 mL), hν 365 nm, 4-7 days.

Fourth, our strategy was shown to operate with a β-(2-quinolyl)acrylic acid derivative **A57**. Among some oligocarboxylic acids in Table 1 tested as an additive, only maleic acid was capable of promoting the [2+2]-photodimerization of β-(2-quinolyl)acrylic acid **A57**, leading exclusively to adduct β**57** (Scheme 3).



Scheme 3. [2+2] photocycloaddition of acid **A57**

Fifth, the high specificity of our simple screening conditions was exemplified by the investigation of acid additives for [2+2]-

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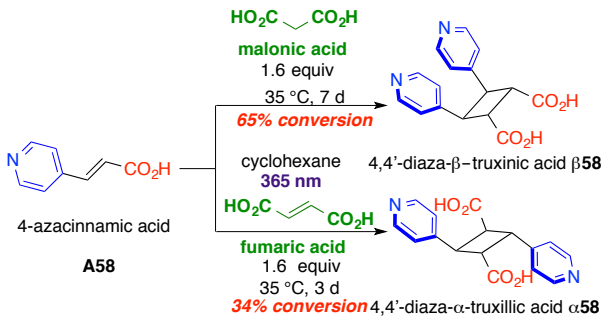
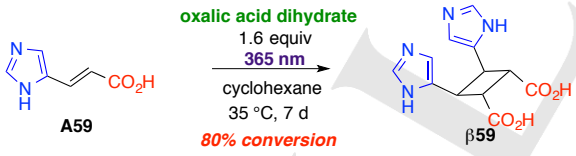
photodimerization of 4-aza-cinnamic acid **A57 (**Scheme 4**)**. While most of the screened additives were found to be totally inactive to promote the photodimerization, we noticed that malonic acid led exclusively to 4,4'-diaza-β-truxinic acid **β57** and fumaric acid resulted in only α-truxillic type dimer **α57**.



Scheme 4. [2+2] Photocycloaddition of **A58**

Finally, our strategy could be applied to unprotected urocanic acid **A59** (Scheme 5). This acid was found in animal sweat and epidermis. When absorbed ultraviolet light, *trans*-urocanic acid is converted *in vivo* to the *cis* isomer and acts as an endogenous sunscreen or photoprotectant against UV-induced DNA damage.[17] Similarly, UV irradiation in solution results in a mixture of *cis* and *trans* isomers whereas irradiation of crystalline urocanic acid produces no photochemical change.[18] While the direct [2+2]-photodimerization of urocanic acid itself has never been achieved, its derivatives were found to be capable of undergoing this transformation in solution[18],[19] or in solid state.[20] A rapid screening of some acid additives mentioned in Table 1 under our conditions of mixing/stirring irradiation led once again to the identification of oxalic as the unique suitable additive to provide exclusively β-truxinic type dimer **β59** in 80% conversion after 7 d of irradiation (Scheme 5).

In all cases of β-substituted acrylic acids, no attempt has been made to isolate the diacid adducts.



Scheme 5. [2+2] Photocycloaddition of urocanic acid **A59**

In order to understand the nature of this procedure, we first attempted to obtain and determine the structure of the expected photoactive cocrystals between 4-stilbazole **A1** and oxalic acid by tentatively performing the cocrystallization in methanol, which is an excellent solvent for both constituting components. Although the desired cocrystals could be isolated, the structural determination of these cocrystals showed that they contained also methanol solvent. Furthermore, these ternary cocrystals were found to be unstable as the solvent residue escaped readily even during the structural determination by X-ray diffraction. We next turned our attention to a solvent-free approach to provide the cocrystals. For this purpose, we performed a sublimation of stilbazole **A1** and oxalic acid under vacuum (0.01 mmHg) at 110-130 °C and allowed the two compounds to condense at lower temperatures. We were able to isolate two kinds of cocrystals **CC1** and **CC2** distinguishable by their different external aspects.

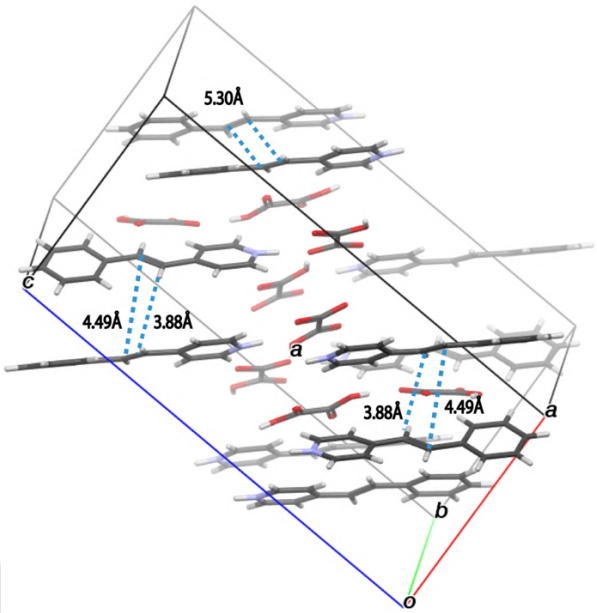


Figure 2. Packing arrangement of stilbazole **A1**-oxalic acid 3:4 cocrystal **CC1** obtained by cocondensation

Structural determination by X-ray diffraction showed that the first crystal **CC1** with stoichiometric ratio 3:4 stilbazole:oxalic acid with head-to-head orientation of two neighboring stilbazole molecules was unsuitable for photocycloaddition due to large distance between two reactive C=C bond (5.30 Å) as well as largely non parallel orientation (4.49 Å and 3.38 Å) (Figure 2).

Interestingly, the second cocrystal **CC2** was a 1:1 complex stilbazole:oxalic acid with head-to-tail orientation between two neighboring stilbazole. The reactive carbon atoms of C=C bond are 4.03 Å and 4.22 Å (Figure 3).[2]

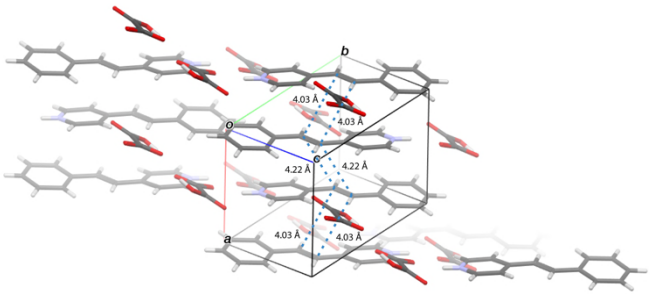


Figure 3. Packing arrangement of stilbazole **A1**-oxalic acid 1:1 cocrystal **CC2** obtained by cocondensation

Although these two crystals are not the only cocrystals that could be formed upon mixing two starting components, one of them are photoactive, leading to **α1** adduct upon irradiation. Moreover, since **A1** and oxalic acid could be moved freely under stirring conditions, the formation of at least one photoactive cocrystal is crucial to the success of our strategy. Indeed, as the

[2+2] photodimerization proceeded for the photoactive cocrystals, new equilibria will be established to rearrange photoinactive cocrystals into inactive one and subsequently into photoadduct. By this way, the conditions for [2+2] photodimerization would be less strict, which requires only a tiny amount of photoinactive cocrystals.

In conclusion, we have reported here a simple and straightforward strategy for rapid screening of additive for selective [2+2] photodimerization of stilbazoles by implementation of irradiation on a mixture of stilbazoles and carboxylic acid additive suspended in a non-polar or moderately polar solvents. Having identified oxalic acid as an excellent additive for most cases, we applied this transformation to a wide range of structurally diverse stilbazoles. Particularly interesting was the ability of our strategy to apply to solid, waxy, amorphous, liquid or even insoluble stilbazoles, making it more powerful to traditional methods. In most cases, the purification of the expected adducts as single isomers in clean reaction mixtures relied principally on the removal of oxalic acid by simply washing with an aqueous solution of $NaHCO_3$. The potential in application to polar olefins bearing many hydrogen bond forming sites has been demonstrated successfully with stilbazoles bearing a free carboxylic acid group as well as some β-hetarylacrylic acids such as 4-azacinnamic acid, β-(2-quinolyl)acrylic acid and urocanic acid. From a more general perspective, we envision that the operational simplicity, broad scope, low cost and scalability of this strategy make it undoubtedly suitable for application in both laboratory and industrial scales.

Experimental Section

A mixture of olefin A (0.2 mmol) and oxalic acid dihydrate (40 mg, 0.32 mmol) in cyclohexane (2 mL) in a 7-mL Pyrex tube was stirred in the photoreactor described in the Supporting Information for 16 h (unless otherwise noted). After removal of cyclohexane, the solid crude reaction mixture was stirred with CH_2Cl_2 (2 mL) and neutralized with an aqueous saturated $NaHCO_3$ solution (2-4 mL). The CH_2Cl_2 layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 mL × 3). The combined organic layers were filtered through a short pad of solid $NaHCO_3$ to afford the desired adduct. See Supporting information for more detail.

Acknowledgements

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Keywords: solid state photodimerization • stilbazole • cyclobutane • keyword 4 • keyword 5

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[14] The insolubility of these carboxylic acid additives were readily observed by gravimetric analysis or by ^{1}H NMR investigation on their saturated solution in cyclohexane-d_{12}.

[15] Compare this result with the formation of **α17** adduct with a previous report (reference 4h) emphasizing the importance of using 1,2,3,4-benzenetetracarboxylic acid as hydrogen bonding template. Reference 4a described the use thiourea as a template to orient olefin **A17** to provide β-truxinic acid type adduct **β17**.

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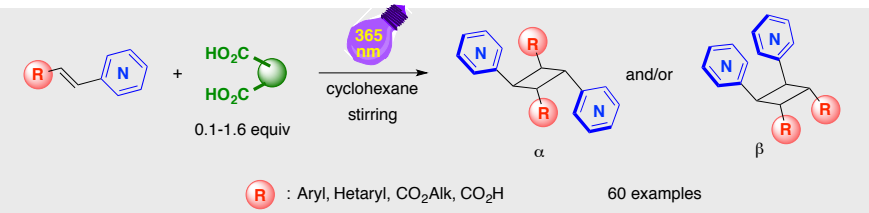

In this study we reported on a very simple technique to perform efficiently photodimerization of some vinylpyridines. By irradiating a stirred mixture of several stilbazoles with solid oxalic acid dihydrate dispersed in a non-polar (*e.g.* cyclohexane) or moderately polar (benzene, dichloromethane, dioxane) solvent, the corresponding dimeric cyclobutane adducts were obtained in high yields with excellent of regio- and stereo- selectivities. The strategy could also be applied successfully to oily, waxy or even insoluble stilbazoles. Moreover, the oxalic acid loading could be lowered to sub-stoichiometric amounts. When further optimizations were needed, our strategy was found to be highly flexible to identify other oligocarboxylic acids as alternative additive to improve or even overturn regioselectivity. Oxalic acid and other oligocarboxylic acids were found to be capable of orienting more than fifty stilbazoles toward photodimerization under these conditions.

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[2 + 2]-Photodimerization of Stilbazoles Promoted by Oxalic Acid in Suspension