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Letter

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Development of Brønsted Base–Photocatalyst Hybrid Systems for Highly Efficient C–C Bond Formation Reactions of Malonates with Styrenes

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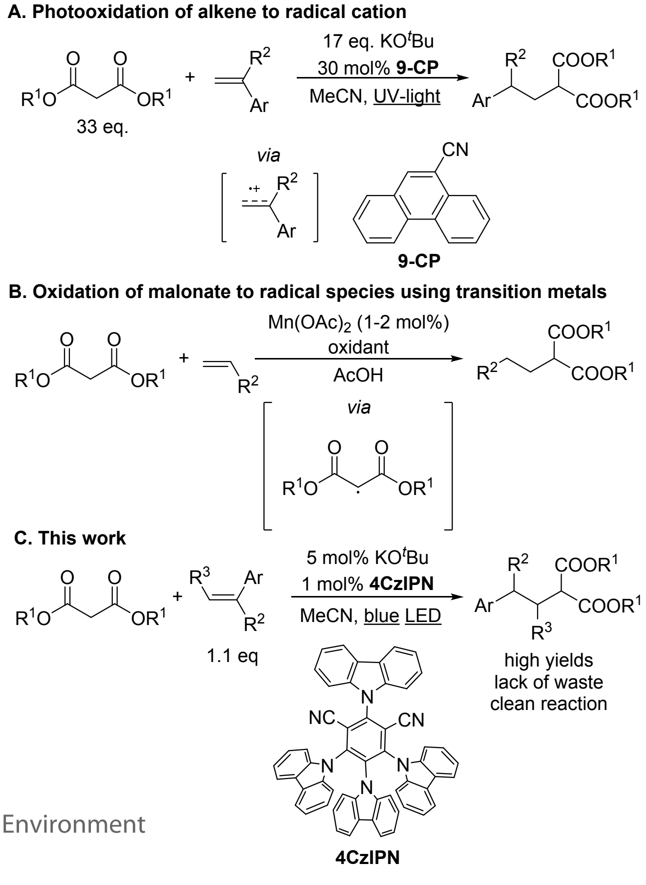
KEYWORDS photocatalysis • hybrid catalysis • Brønsted base • malonates • radical process.

ABSTRACT: Brønsted base–photocatalyst hybrid systems have been developed for reactions of malonates with styrene derivatives. The concept of this process lies in the photooxidation of catalytic amounts of the enolate to form reactive radicals that react with alkene double bonds under mild reaction conditions. This is an example of visible light activated C–C bond formation reactions of malonates with alkenes to realize high atom economy under very mild reaction conditions without using any transition metal catalysts.

Nucleophilic addition of carbanions to alkenes is recognized as one of the most efficient C–C bond formation reactions.[1,2] In particular, when carbanions are generated from stable and readily available precursors using catalysts, the process is ideal in terms of atom economy since simple proton transfer occurs from starting materials to products via catalytic amounts of carbanions. Malonic acid esters (malonates) are readily available and their functional groups can be easily converted into the desired target molecules; thus, they are often employed as precursors of carbanions. While the corresponding enolates are known to be stabilized carbanions, their nucleophilicity is generally not sufficient for reactions with alkenes without any electron-withdrawing groups (simple alkenes). Reactions of malonates with such alkenes catalyzed by transition metals have been investigated; however, stoichiometric amounts of Brønsted bases are needed in most cases.[3] Towards truly efficient catalytic processes, we focused on the development of reactions of malonates with alkenes that proceed through the formation of radicals using catalytic amounts of Brønsted base and redox activator without using any transition metal catalysts.

Although reactions of malonates with simple alkenes via single-electron photooxidation (SET) have been reported, strong UV-light and the use of a large excess of base and malonate are required (Scheme 1A).[4,5] On the other hand, reactions of 1,3-dicarbonyl radicals generated via SET with alkenes promoted by a catalytic amount of $Mn(OAc)_2$ and a stoichiometric amount of oxidant was disclosed; however, acetic acid was needed as a solvent and applicable substrates were limited

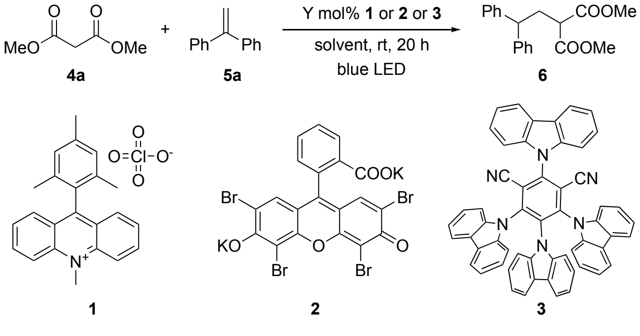


(Scheme 1B).[6,7] We envisioned that modern visible-light photocatalysis would be applicable to these types of reactions.

Scheme 1. Alkylation reactions of malonates with alkenes**.** To date, a variety of metal and organophotocatalysts have been developed and employed in radical-mediated reactions.[8] However, these photocatalysts are not stable and their photoactivity is significantly decreased under basic conditions. Therefore, the effects that visible-light photocatalysts have on Brønsted base-catalyzed reactions remain unclear. Here, we have developed effective Brønsted base–photocatalyst hybrid systems for catalytic alkylation reactions of malonates with less electrophilic alkenes and realized high atom economy under very mild reaction conditions without using any transition metal catalysts (Scheme 1C).

The reaction of dimethyl malonate (**4a**) with 1,1′-diphenylethene (**5a**) was selected as a model reaction in the presence of KO^{t}Bu as a base and photocatalysts **1**–**3** at room temperature (rt) in MeCN (Table 1). Whereas photocatalysts **1** and **2** gave the product **6** in low yields (entries 1 and 2), photocatalyst **3** provided **6** in 87% yield (entry 3). Further optimization of the reaction conditions enabled a decrease in the amount of the base and **3** to 5 and 1 mol%, respectively (entries 4–6). The target reaction proceeded only in polar solvents such as MeCN and THF (entries 4, 7–9). For further optimization, we examined the use of organic photosensitizers to ensure that **3** delivered the best results (see Table S1 in the Supporting Information (SI)).

Table 1. Optimization of reaction conditions for the reaction of **4a** with **5a**

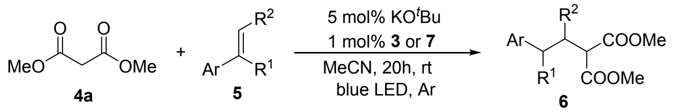


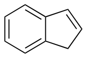
Entry	Photocatalyst	Solvent	X amount	Y amount	Yield (%)
1[a]	1	MeCN	30 mol%	3 mol%	0[b]
2[a]	2	MeCN	30 mol%	3 mol%	5[b]
3[a]	3	MeCN	30 mol%	3 mol%	87[b]
4[c]	3	MeCN	5 mol%	1 mol%	91[d]
5[c]	3	MeCN	5 mol%	0.5 mol%	79[d]
6[c]	3	MeCN	2 mol%	1 mol%	77[b]
7[c]	3	THF	5 mol%	1 mol%	76[d]
8[c]	3	DCM	5 mol%	1 mol%	20[d]
9[c]	3	Toluene	5 mol%	1 mol%	0[b]

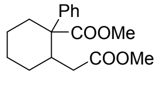
[a] Reaction conditions: **4a** (0.3 mmol), **5a** (0.3 mmol), KO^{t}Bu (0.1 mmol), and photocatalyst (0.01 mmol) in anhydrous MeCN (5.0 mL) under argon at rt irradiated with 24W blue LED for 20 h; [b] Determined by ^{1}H NMR analysis with CH_2Br_2 as internal standard; [c] Reaction conditions: **4a** (0.3 mmol), **5a** (0.33 mmol), KO^{t}Bu, and **3** as described, in anhydrous solvent (5.0 mL) under argon at rt irradiated with 24W blue LED for 20 h; [d] Isolated yield.

We next surveyed the scope of the reaction with respect to alkenes under the optimized reaction conditions. It was found that 1,1-diarylethylene derivatives **5a**–**e** afforded the desired products **6** in excellent yields (Table 2, entries 1–5). Notably, after simple work-up, an almost pure product was identified in the reaction mixture, with only **3** and trace amounts of starting materials being observed (see ^{1}H NMR spectra of crude samples in the Supporting Information). An exception was **5f**, bearing two strong electron-donating groups on Ar and R^1 (entry 6). The R^2-substituted alkenes **5g**–**i** also gave lower yields (entries 7–9). While styrene **5j**, its alkyl substituted derivatives **5k**, **5l**, and those with electron-donating groups (**5m**, **5n**) were reactive substrates under the standard reaction conditions (entries 10–12, see also Table S2 in the Supporting Information), the yields were significantly improved by using photocatalyst **7** instead of **3** (Table 2, in parentheses). The effects of **3** and **7** were investigated as part of a subsequent consideration of the mechanism (see below). Styrenes with electron-withdrawing groups **5o**–**t** reacted smoothly using **3** (entries 13–20). Whereas only a trace amount of product **6au** was obtained in the reaction of α-methylstyrene **5u** using **3**, 77% yield of **6au** was obtained using **7** (entry 21). The high reactivity was also observed for alkenes **5v**–**zb** bearing heterocyclic rings, except for **5y** (entries 22–28). For the latter alkene and for non-terminal alkenes **5zc**[9] and **5zd**, better yields of the desired products were obtained using photocatalyst **7** (entry 25 in parenthesis, entries 29, 30). Interestingly, in case of styrenes **5p** and **5j** (only when **7** was used) the side products of double addition of alkene to malonate have been detected (see, Scheme S3 in the Supporting Information).

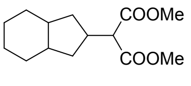
Table 2. Scope and limitations of the reaction with alkenes^a



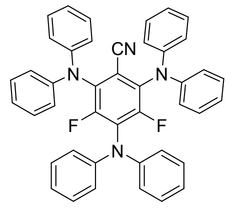
Entry	Ar	R^1	R^2	5	6	Yield
1	Ph	Ph	H	**5a**	**6aa**	91
2	*p*-tol	Ph	H	**5b**	**6ab**	97
3	*p*-	Ph	H	**5c**	**6ac**	95
4	*p*-BrC$_6$H$_4$	Ph	H	**5d**	**6ad**	87
5	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	H	**5e**	**6ae**	95
6	*p*-	*p*-	H	**5f**	**6af**	17^c
7	Ph	Ph	Me	**5g**	**6ag**	37
8	*p*-FC$_6$H$_4$	*p*-FC$_6$H$_4$	Me	**5h**	**6ah**	30
9	Ph	Ph	Ph	**5i**	**6ai**	17
10	Ph	H	H	**5j**	**6aj**	27 (77)^{d,e}
11	*p*-tol	H	H	**5k**	**6ak**	21 (71)^e
12	*p*-^{t}BuC$_6$H$_4$	H	H	**5l**	**6al**	10 (64)^e
13	*p*-MeOC$_6$H$_4$	H	H	**5**	**6am**	0 (28)^e
14	*m*-MeOC$_6$H$_4$	H	H	**5n**	**6an**	0^c (78)^e
15	*p*-ClC$_6$H$_4$	H	H	**5o**	**6ao**	43 (80)^e
16	*p*-O$_2$NC$_6$H$_4$	H	H	**5p**	**6ap**	55
17	*o*-O$_2$NC$_6$H$_4$	H	H	**5q**	**6aq**	60
18	*p*-NCC$_6$H$_4$	H	H	**5r**	**6ar**	56
19	*p*-AcC$_6$H$_4$	H	H	**5s**	**6as**	45
20	*p*-MeO$_2$CC$_6$H$_4$	H	H	**5t**	**6at**	94
21	Ph	Me	H	**5u**	**6a**	trace^c (77)^e
22	2-pyridyl	H	H	**5v**	**6av**	80
23	2-pyridyl	Me	H	**5w**	**6aw**	49
24	2-pyridyl	Ph	H	**5x**	**6ax**	99
25	3-pyridyl	H	H	**5y**	**6ay**	11 (46)^e
26	4-pyridyl	H	H	**5z**	**6az**	85
27	2-quinolyl	H	H	**5z**	**6aza**	51
28	3-quinolyl	H	H	**5z**	**6azb**	41
29	Ph	-(CH$_2$)$_4$-		**5z**	**6azc**	14 (70)^e
30				**5zd**	**6azd**	15 (59)^e



6azc



6azd



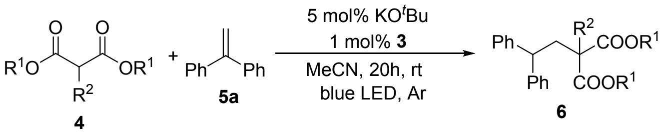
(3DPA2FBN) **7**

^{a} Reaction conditions: **4a** (0.3 mmol), **5a–azi** (0.33 mmol), KO^{t}Bu (0.015 mmol), **3** (0.003 mmol, Method A) in anhydrous MeCN (5.0 mL) under argon at rt irradiated with 24W blue LED for 20 h. ^{b} Isolated yield unless otherwise noted. ^{c} Determined by ^{1}H NMR analysis with CH$_2$Br$_2$ as internal standard. ^{d} 1.1 equiv. of **4a** was used. ^{e} Photocatalyst **7** was used instead of **3**.

Next, we investigated the scope of the reaction with malonates **4b–f**. Whereas aliphatic esters gave nearly quantitative yields of the expected products **6ba–da**, low reactivity was observed for **4e** (both substrates remained in the reaction mixture), and substitution at the methylene group also inhibited the process (Table 3). The lack of reactivity of **4f** may be rationalized by formation of stable tertiary radical species (see further mechanistic discussion), thus thermodynamic force for its recombination with alkene is significantly decreased. In addition, other 1,3-dicarbonyl compounds like diketones or ketoesters in the developed conditions undergo competitive DeMayo reactions resulting in complex product mixture formation. Moreover, the visible-light activated DeMayo reaction in comparable conditions for those substrates has been reported by König recently.[10]

A plausible mechanism for the reaction is outlined in Scheme 2. The visible-light-excited photocatalyst [Photocat]* oxidizes enolate **I**, resulting in the formation of radical **II**, which undergoes recombination with alkene **5** to form radical **III**. Comparison of the oxidation potentials for **5a** [$E(\mathrm{P/P^{\bullet+}})$ = +1.82 V vs. SCE in MeCN],[11] enolates of malonates [ca. 0–0.6 V (for example **4b** $E(\mathrm{P^{-}/P^{\bullet}})$ = +0.59 V vs. SCE in MeCN)[12]] and photocatalyst **3** [$E(\mathrm{P^{*}/P^{\bullet-}})$ = +1.35 V and $E(\mathrm{P/P^{\bullet-}})$ = –1.21 V vs. SCE in MeCN][13] suggested that an electron-transfer event was thermodynamically more feasible for the enolate than for the alkene. Similar observations and conclusions supported by spectroscopic and CV measurement verification were reported by König.[10]

Table 3. Scope and limitations of the reaction with malonates^a



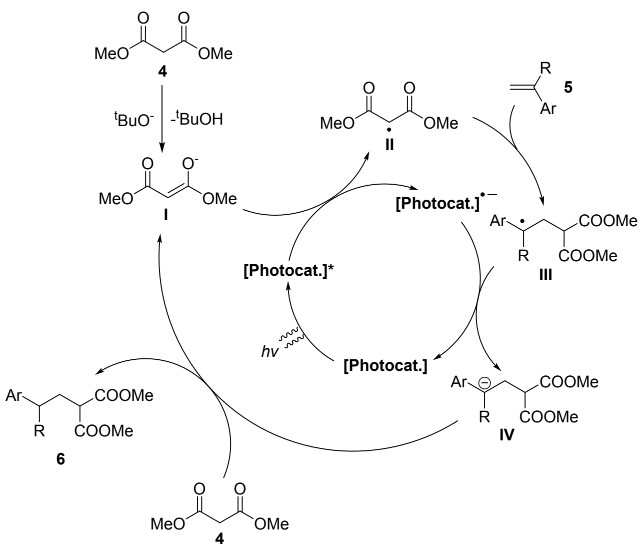
Entry	R^1	R^2	4	6	Yield (%)^b
1	Et	H	**4b**	**6ba**	94
2	^{i}Pr	H	**4c**	**6ca**	99
3	^{t}Bu	H	**4d**	**6da**	92
4	Allyl	H	**4e**	**6ea**	18^c
5	Me	Me	**4f**	**6fa**	0^c

[a] Reaction conditions: **4b–i** (0.3 mmol), **5a** (0.33 mmol), KO^{t}Bu (0.015 mmol), **3** (0.003 mmol), in anhydrous MeCN (5.0 mL) under argon at rt irradiated with 24W blue LED for 20 h. [b] Isolated yield unless otherwise noted. [c] Determined by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

Diarylalkenes result in the formation of highly stable dibenzyl tertiary radicals, which is reflected in the high yields of products. Newly formed radical **III** is reduced to carbanion **IV** to regenerate photocatalyst **3**. Further deprotonation of another molecule of **4a** by product-base **IV** completes the catalytic cycle. When the reaction was conducted in deuterated solvent (CD_3CN) no deuterium incorporation was found in the final product **6** structure, which excludes the possibility of solvent participation in proton or hydrogen atom transfer (see Table S4 in the Supporting Information).[14]

On the other hand, judging from the results presented in Table 2, it was noted that some yields were influenced by the reduction potential of the benzyl radicals to the corresponding carbanions.

Scheme 2. Proposed mechanism based on the conducted investigation



Benzyl radicals bearing electron-withdrawing groups on the aromatic rings have higher reduction potentials [**5r** (56% yield) (P•/P–) = –0.77 V; **5s** (45% yield) (P•/P–) = –0.71 V; **5o** (43% yield) (P•/P–) = –1.40 V vs. SCE in MeCN] than those with electron-donating groups [**5m** (0% yield) (P•/P–) = –1.82 V; **5k** (21% yield) (P•/P–) = –1.62 V; **5j** (27% yield) (P•/P–) = –1.43 V vs. SCE in MeCN] due to the destabilizing/stabilizing effect of substituents.[15] These results suggested that a second electron-transfer process that provided **IV** along with regeneration of photocatalyst **3** might be a rate-limiting step. Photocatalyst **7** improved the low yields of the reactions with styrene bearing electron-donating substituents, since **7** was reported to possess a higher ground-state reduction potential [(P/P•–) = –1.92 V vs. SCE in MeCN].[16]

In summary, we have developed a Brønsted base–photocatalyst hybrid system that enabled reactions of malonates with styrene derivatives. The reactions proceeded cleanly with low loadings of base and photocatalyst. Light-initiated single-electron transfer oxidation of in situ generated enolates forming radicals is one of the key steps. This is the first example of C–C bond formation reactions of malonates with alkenes to realize high atom economy under very mild reaction conditions without using any transition metal catalysts.

ASSOCIATED CONTENT

Supporting Information

This supporting information is available free of charge at http://pubs.acs.org.
Materials, photoreactor structure, supporting experiments, experimental methods, compounds characterization data

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

SET, single electron transfer, CV, cyclic voltammetry, SCE, saturated calomel electrode, TLC, thin layer chromatography, NMR nuclear magnetic resonance, LED, light-emitting diode

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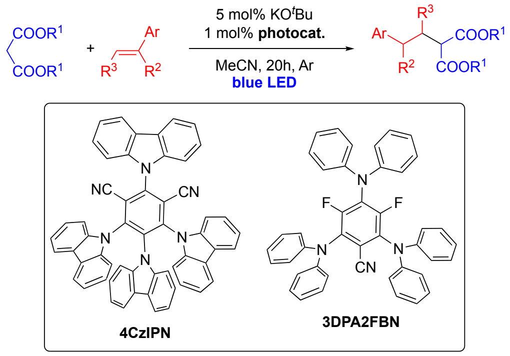
COOR^1
COOR^1
+
Ar
R^3
R^2
5 mol% KO^{t}Bu
1 mol% photocat.
MeCN, 20h, Ar
blue LED
Ar
R^3
COOR^1
R^2
COOR^1
NC
CN
N
4CzIPN
F
F
CN
N
3DPA2FBN