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Enantioselective Intermolecular [2+2] Photocycloaddition Reactions of 2(1*H*)-Quinolones Induced by Visible Light Irradiation

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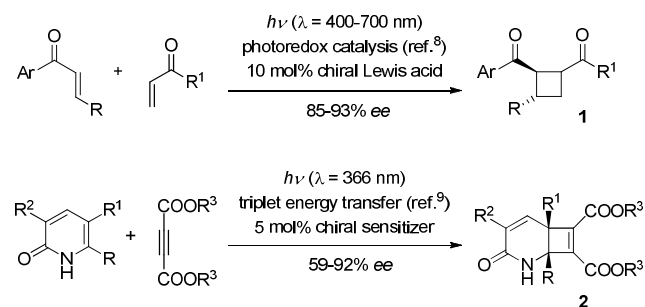
Supporting Information Placeholder

ABSTRACT: In the presence of a chiral thioxanthone catalyst (10 mol%) the title compounds underwent a clean intermolecular [2+2] photocycloaddition with electron deficient olefins at $\lambda = 419$ nm. The reactions proceeded not only with excellent regio- and diastereoselectivity but delivered the respective cyclobutane products also with significant enantiomeric excess (up to 95% *ee*). Key to the success of the reactions is a two-point hydrogen bonding between quinolone and catalyzenabling efficient energy transfer and high enantioface differentiation. Preliminary work indicated that solar irradiation can be used for this process and that the substrate scope can be further expanded to isoquinolones.

The [2+2] photocycloaddition reaction¹ has emerged over the last decades as a powerful tool in organic synthesis² and offers a straightforward access to cyclobutanes generating up to four stereogenic centers in a single transformation. Intermolecular [2+2] photocycloaddition reactions offer a wide flexibility regarding the choice of substrates but frequently suffer from relatively poor regio- and stereocontrol.¹ In contrast to thermal cycloaddition reactions, the intermediate of a [2+2] photocycloaddition is short-lived and requires efficient trapping by its reaction partner.³ In recent years, interest in enantioselective photochemical reactions has significantly increased and it is therefore not surprising that attempts have been made to perform the reaction enantioselectively by the use of a chiral auxiliary or a chiral template.⁴ Catalytic enantioselective photochemical reactions⁵ are still scarce, however, and Scheme 1 provides the two only examples, in which notable enantioselectivities were achieved in an intermolecular [2+2] photocycloaddition reaction^{6,7} under catalytic conditions. The first example, which led to the formation of cyclobutanes **1**, was reported in 2014 by the Yoon group.⁸ Its characteristic feature is the use of a ruthenium photoredox catalyst under visible light conditions, which generates in the presence of a chiral Lewis acid a radical anion that in turn can add enantioselectively to another enone. The relative configuration of the products could be controlled by the chiral ligand of the Lewis acid. In the same year it was found by our group that triplet energy transfer is a viable concept for asymmetric induction by a chiral triplet sensitizer in the intermolecular addition of pyridones to certain alkynes.⁹ The catalyst was a chiral xan-

thone, which required irradiation by UV-A light ($\lambda = 366$ nm).

Scheme 1. Previous Work on Enantioselective Intermolecular [2+2] Photocycloaddition Reactions

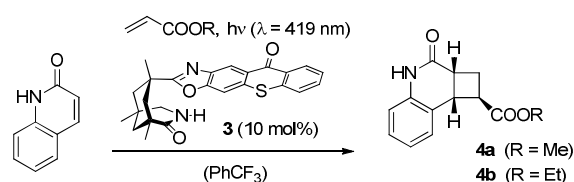


In the present study, we have attempted to apply a chiral sensitizer to an intermolecular [2+2] photocycloaddition under visible light irradiation. We found the title compounds to be suitable substrates to react with a variety of olefins upon sensitization with a chiral thioxanthone at $\lambda = 419$ nm. Enantioselectivities exceeded in several cases 90% *ee* and it was possible to substantiate the hypothesis that the reaction rate of the respective olefin with the photoexcited substrate is decisive for a successful chirality transfer. Our preliminary results are summarized in this communication.

Initial work was performed with parent 2(1*H*)-quinolone¹⁰ as the substrate and methyl or ethyl acrylate as the reaction partner (Table 1). Previous experiments on the intramolecular [2+2] photocycloaddition reaction of quinolones had shown that the reactions are best performed at a concentration of $c = 2.5$ mM in trifluorotoluene solution and with 10 mol% of the catalyst.^{7a,b,e,f} As in most intermolecular [2+2] photocycloaddition reactions, the photochemically inactive olefin was used in excess to avoid [2+2] photodimerization. The triplet energy of 2(1*H*)-quinolone is tabulated as 276 kJ mol⁻¹ and seemed sufficiently close to the triplet energy of thioxanthenes¹¹ to expect an energy transfer. This expectation was gratifyingly confirmed, as a smooth reaction was observed already with 10 equivalents of methyl acrylate at $\lambda = 419$ nm.¹² The reaction was complete after ten hours and product **4a**¹³ was obtained in 74% *ee*. Remarkably, the regio- and simple diastereoselectivity of the reaction was high and a single isomer was obtained. The product is the formal head-

to-tail (HT) product¹⁴ with the methoxycarbonyl substituent in *exo*-position. An increase in the number of acrylate equivalents (entries 1-3) led to an increase in rate and an increase in enantioselectivity. The reaction with 50 equivalents of methyl acrylate was complete after six hours and delivered the product with 81% *ee*. A further raise of the olefin concentration was not attempted for practical purposes (removal of excess olefin, olefin polymerization, solubility). A decrease in temperature to -40 °C turned out to be equally impractical as the rate decreased significantly (entry 4). The same observation was made for ethyl acrylate (entries 5, 6), which delivered at -40 °C a slightly improved enantioselectivity for product **4b** at the expense of space-time yield. There was no background reaction in the absence of a sensitizer (entry 7), which indicated that the thioxanthone is involved in the catalytic cycle (*vide infra*).

Table 1. Optimization of the Catalytic Enantioselective [2+2] Photocycloaddition of 2(1*H*)-Quinolone with Acrylates



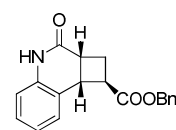
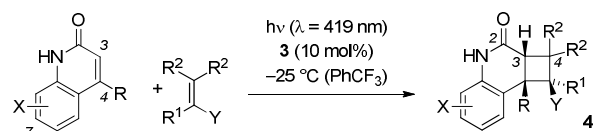
entry	R	eq. (alkene)	t (h) ^a	temp. (°C)	product	yield (%) ^b	<i>ee</i> (%) ^c
1	Me	10	10	-25	4a	79	74
2	Me	20	7	-25	4a	74	80
3	Me	50	6	-25	4a	76	81
4	Me	50	22	-40	4a	85	83
5	Et	50	6	-25	4b	82	78
6	Et	50	45	-40	4b	79	80
7 ^d	Et	50	24	-25	4b	—	—

^aIrradiation time at $\lambda = 419$ nm in trifluorotoluene solution ($c = 2.5$ mM). ^bYield of isolated product. ^cThe enantiomeric excess was calculated from the ratio of enantiomers (**4ent-4**) as determined by chiral HPLC analysis. ^dNo thioxanthone (**3**) was added to the reaction mixture.

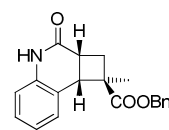
Further studies were concerned with a preliminary evaluation of the substrate scope (Table 2). Expectedly, the ester substituent at the acrylate did not change yield or enantioselectivity and the benzyl acrylate [2+2] photocycloaddition product **4c** was obtained in 83% yield and 82% *ee*. A positive influence on the enantioselectivity was noted upon employing an α -substituted acrylate (product **4d**) or a stronger electron withdrawing group at the olefinic double bond. Indeed, methyl vinyl ketone and ethyl vinyl ketone turned out to be excellent olefin components, providing the quinolone products **4e** and **4f** with enantioselectivities exceeding 90% *ee*. Methyl substitution at the β -position of the α,β -unsaturated ketone had little impact on the enantioselectivity (product **4g**) but the reaction remained incomplete even after an irradiation time of eight hours. 4-Pentylquinolone reacted smoothly with methyl vinyl ketone to produce product **4h** (94%, 90% *ee*). Methyl substitution was further probed at

positions C₅ to C₈ of the quinolone core (products **4i**, **4k**, **4l**, **4n**).

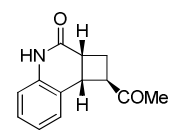
Table 2. Influence of Substituents on the Catalytic Enantioselective [2+2] Photocycloaddition Reactions between 2(1*H*)-Quinolones and Olefins^a



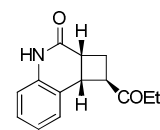
4c^b (79%) 80% *ee*



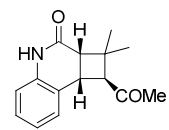
4d (66%) 90% *ee*



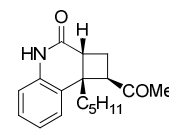
4e (80%) 91% *ee*



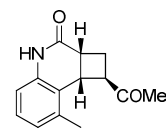
4f^b (89%) 91% *ee*



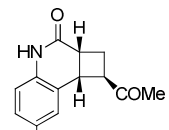
4g (47%) 88% *ee*



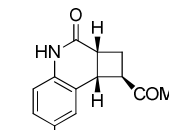
4h (94%) 90% *ee*



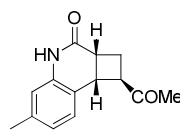
4i (48%) 91% *ee*



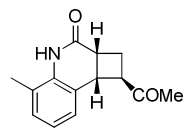
Br **4j** (59%) 94% *ee*



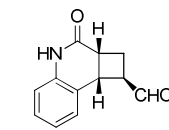
4k (71%) 85% *ee*



4l (72%) 95% *ee*



4m (68%) 80% *ee*

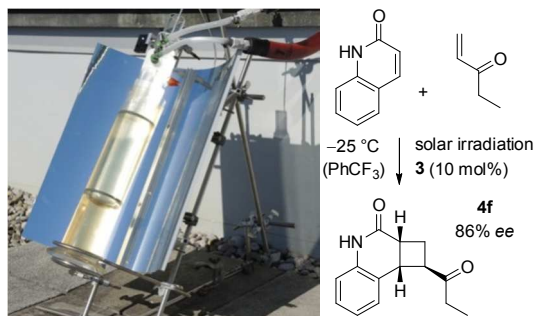


4n (44%) 91% *ee*

^a Irradiation times varied between six and 18 hours. The reactions were performed on a scale of 25 μ mol. For detailed information, see the SI. ^bThe reaction was performed on a scale of 0.15 mmol.

Enantioselectivities remained high and reached a peak for substitution at position C₇ with product **4l** being formed in 95% *ee*. A decrease in selectivity was noted for product **4m** derived from 8-methylquinolone. Notably, the [2+2] photocycloaddition was compatible with a bromine substituent at the quinolone core (product **4j**). Even the sensitive olefin acrolein could be brought to react in the enantioselective [2+2] photocycloaddition. Product **4n** was isolated in 44% yield and with 91% *ee*.

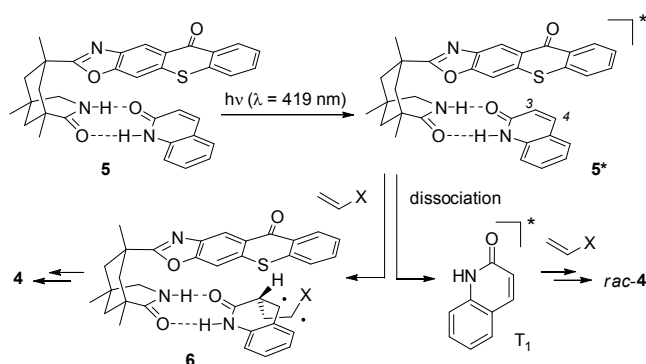
Scheme 2. Apparatus for Solar Irradiation and Result of an Intermolecular [2+2] Photocycloaddition



Given the fact that visible light enables the enantioselective [2+2] photocycloaddition it seemed desirable to attempt the reaction also with solar irradiation. A parabolic reflector was employed to focus the sun beam on the reaction vessel (Scheme 2). A Fe₂(SO₄)₃ filter solution¹⁵ was applied to avoid undesired direct excitation by short wavelength photons. Due to the low sunlight intensity in winter, the reaction was slower than with the artificial light sources. After three hours, the yield for **4f** was 81% at 21% conversion but the enantioselectivity remained high (86% ee).

The absolute configuration of the photocycloaddition products was derived from their specific rotation. It has been earlier reported that the helical arrangement of the conjugated π -system in dihydro-2-quinolones is responsible for the chiroptical properties of this compound class.^{7b,16} The specific rotation of 3,6-dihydrocyclobuta[c]-2-quinolones **4b**, **4c**, **4d**, **4f**, and **4j** was determined and they were found to be levorotatory suggesting an (*R*)-configuration at carbon atom C₃ (Scheme 2). This absolute configuration indicates an attack at the prostereogenicquinolone carbon atom C₃ from the *Re* face. Indeed, based on previous results,^{7b,e} it is assumed that quinolone is excited into its reactive triplet state by triplet energy transfer in complex **5** (Scheme 3). In line with the mode of action of related templates,¹⁷ the approach to the photoexcited quinolone in **5*** is only feasible for the olefin to occur from the *Re*(bottom) face relative to carbon atom C₃ leading to the putative 1,4-diradical **6**, from which product formation occurs by C-C bond formation at C₄.

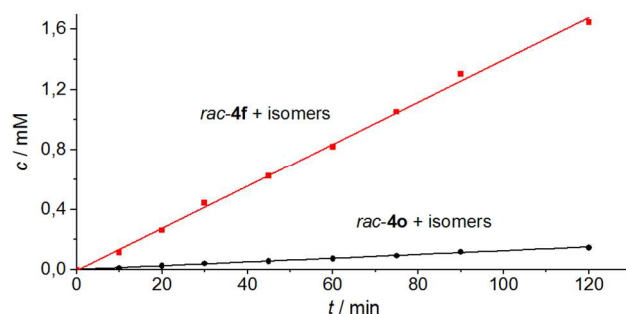
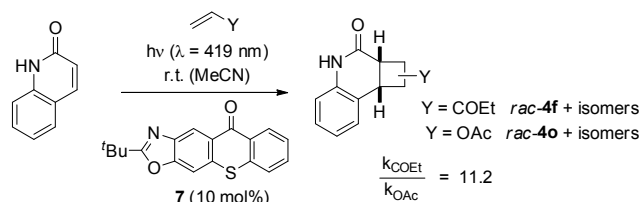
Scheme 3. Mechanistic Picture of the Enantioselective [2+2] Photocycloaddition and Origin for the Formation of Racemic Product *rac*-**4**



We have previously speculated that dissociation of the triplet quinolone (T₁) from complex **5*** leads to a deterioration of the enantioselectivity as the former species will not encounter any asymmetric induction thus forming racemic products *rac*-**4**.^{7b} In the present reactions, we noted that

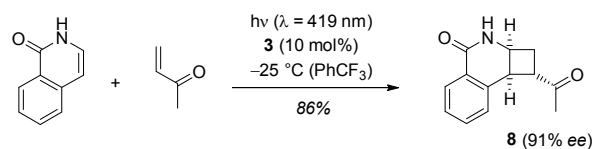
more electron rich olefins such as vinyl acetate produced the respective products with lower selectivity. Product **4o**^{10c} was the formal HT product of the vinyl acetate [2+2] photocycloaddition to quinolone and was formed as an *exo/endo* mixture. Under the conditions given in Scheme 2, the *exo*-product (42% yield) was obtained with 58% ee, and the *endo*-product (36% yield) with 43% ee. In order to support the hypothesis that a lower reaction rate might be responsible for the decrease in enantioselectivity as compared for example to product **4f** (92% ee), a competition experiment was performed (Scheme 4). The reaction was conducted at room temperature in acetonitrile solution, which facilitated the isolation and quantification of suitable samples in short time intervals. Triplet sensitization was achieved with the *tert*-butyl analogue **7** (10 mol%) of the chiral catalyst **3**.

Scheme 4. Competing Intermolecular [2+2] Photocycloaddition of Vinyl Acetate vs. Ethyl Vinyl Ketone and 2(*1H*)-Quinolone



One equiv. of parent 2(*1H*)-quinolone were reacted in the presence of 25 equiv. of vinyl acetate and ethyl vinyl ketone. Product analysis was performed by GLC employing dodecane as internal standard. It is evident from the rate profile (Scheme 4) that formation of product *rac*-**4f** was significantly faster than formation of product *rac*-**4o**. Quantification of the data delivered a relative reaction rate $k_{\text{COEt}}/k_{\text{OAc}}$ of 11.2 in favor of the former reaction, which is in line with the higher enantioselectivity obtained with ethyl vinyl ketone as olefinic reaction partner. If steric hindrance interferes with the hydrogen bonding event, the enantioselectivity of the [2+2] photocycloaddition can also decrease. The comparably low enantioselectivity for product **4m** (Table 2) is likely due to the methyl group at carbon atom C₈ of the quinolone core.

Scheme 5. Enantioselective Intermolecular [2+2] Photocycloaddition of 1(2*H*)-Isoquinolone and Methyl Vinyl Ketone



The kinetic data show that insufficient enantioface differentiation in complex **5*** is not responsible for a lack of enantioselectivity with certain olefins but their low reaction rates. With this in mind, other substrates which contain a lactam binding motif and which show a high intermolecular reaction rate should be equally suitable for enantioselectively catalyzed intermolecular [2+2] photocycloaddition reaction. A preliminary experiment with parent 1(2*H*)-isoquinolone¹⁹ and methyl vinyl ketone revealed that a high enantioselectivity can be achieved also with isoquinolone substrates (Scheme 5). Product **8**^{17d} was obtained as a single isomer in 91% *ee*. The conversion remained incomplete after nine hours and varying amounts of starting material were recovered. In the best case, the conversion was 86% and the yield of product was 74% (86% based on conversion).

In summary, chiral thioxanthone **3** was shown to be a competent catalyst to mediate the enantioselective intermolecular [2+2] photocycloaddition of various quinolones and electron deficient alkenes. Association between the catalyst and the substrate by hydrogen bonding is critical for the success of the reaction and dissociation of the photoexcited substrate from the catalyst is likely responsible for a loss in enantioselectivity as observed for vinyl acetate as the reaction partner. The kinetic parameters of these processes are currently being studied in more detail and will be reported together with possible applications of the enantioselective [2+2] photocycloaddition in due course.

Supporting Information

Experimental procedures, analytical data for all new compounds, proof of constitution and configuration, competition experiment, NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

[†]These authors contributed equally to the project.

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(11) The triplet energy (E_T) of parent thioxanthone is tabulated as $E_T = 265 \text{ kJ mol}^{-1}$ (Murov, S. L., Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*, 2nd ed., Dekker: New York, 1993, p. 80).

(12) For an emission spectrum of the irradiation lamps, see ref.^{7f}.

(13) All compounds **4a-4n** have not yet been reported and were therefore prepared in racemic form for comparison (see Supporting Information).

(14) Parent 2(1*H*)-quinolone (carbonyl) has been previously reported to react with acrylonitrile exclusively to the HT product: (a) ref.^{10c}. (b) Lewis, F. D.; Reddy, G. D.; Elbert, J. E.; Tillberg, B. E.; Meltzer, J. A.; Kojima, M. *J. Org. Chem.* **1991**, *56*, 5311-5318.

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