Photochemistry

DOI: 10.1002/anie.201310997

A Chiral Thioxanthone as an Organocatalyst for Enantioselective [2+2] Photocycloaddition Reactions Induced by Visible Light**

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Abstract: *Thioxanthone **1**, which was synthesized in a concise fashion from methyl thiosalicylate, exhibits a significant absorption in the visible light region. It allows for an efficient enantioselective catalysis of intramolecular [2+2] photocycloaddition reactions presumably by triplet energy transfer.*

One of the most fascinating aspects of photochemistry is the fact that visible light can potentially be used to drive chemical transformations. Many photochemical textbook reactions, for example, the [2+2] photocycloaddition[1] or the Paternò–Büchi reaction,[2] originate from irradiation experiments performed with sunlight. With the advent of artificial light sources, however, UV irradiation became common practice in photochemistry and replaced visible light irradiation sources.[3] Indeed, for many important chromophores (carbonyl compounds, enones, arenes, etc.) direct excitation requires a wavelength region of $\lambda = 250$–350 nm, which is nicely covered by medium-pressure mercury lamps. Despite the high efficiency of photochemical reactions occurring in the UV region, it is important to realize that the energy of a $\lambda =$ 400 nm photon corresponds to about 300 kJ mol^{-1}, which is significantly higher than the triplet energy of many photochemical substrates. If suitable sensitizers are found, and they are competent of transferring light energy to these substrates, visible-light irradiation can be similarly or even more effective than direct UV excitation. Along these lines, Yoon et al. have recently reported that an iridium complex with a triplet energy (E_T) of 255 kJ mol^{-1} is capable of sensitizing the intramolecular [2+2] photocycloaddition reaction of certain styrenes ($E_T \leq 250$ kJ mol^{-1}).[4] The catalyst loading was low (1 mol %) and reaction yields were high if the reaction was performed in a polar solvent (DMSO). A drawback of this specific transformation—as of many other [2+2] photocycloaddition reactions[5]—is the fact that it produces exclusively racemic products from prochiral substrates. Indeed, the control of absolute product configuration in photochemical reactions remains a considerable challenge[6] given that these reactions proceed at an energy hypersurface which is high above the ground state and which does not involve significant activation barriers. We now report on the synthesis of the chiral thioxanthone **1** (for structure see Scheme 1), which absorbs visible light and which has the potential to act as an effective catalyst for triplet-sensitized reactions. It was shown that [2+2] photocycloaddition reactions of 4-(pent-4-enyl)quinolones and their heteroatom analogues proceed with high enantioselectivity[7] in the presence of this catalyst.

Compared to xanthones, thioxanthones show a bathochromic shift in their UV/Vis spectra. Typically, their absorption maximum is centered at $\lambda_{max} \approx 390$ nm with a significant absorption in the visible region (see below). The triplet energy of parent thioxanthone has been determined as 264 kJ mol^{-1} versus 310 kJ mol^{-1} for xanthone.[8] Based on the above-mentioned considerations and based on our successful work with a chiral xanthone as sensitizer,[9] it seemed promising to prepare a chiral thioxanthone which would incorporate a related hydrogen-bonding motif. Starting from the thioether **2**, which was accessible by nucleophilic substitution of readily available 3-isopropoxy-4-nitrofluorobenzene[10] with methyl thiosalicylate,[11] the thioxanthone ring was closed upon saponification of the ester group by an intramolecular Friedel–Crafts acylation (Scheme 1).[9a] Removal of the isopropyl group converted the arylether **3** into alcohol **4**, which was linked to the activated acid *rac*-**5** via its mixed anhydride. Cyclization of the aromatic *ortho*-nitroester *rac*-**6** was achieved with thionyl chloride after reduction to the respective aniline with tin(II) chloride. Eventually, separation of the two enantiomers, **1** and *ent*-**1**, was performed by semipreparative HPLC using a chiral stationary phase.

The thioxanthone **1** is a yellow-colored compound, the UV/Vis spectrum of which exhibits a maximum at $\lambda_{max} =$ 387 nm with a molar absorption coefficient $\varepsilon = 4540\,\text{M}^{-1}\,\text{cm}^{-1}$ (Figure 1). Although its triplet energy has not yet been determined, it is evident from photostability studies that the triplet state of **1** is less aggressive towards hydrogen abstraction[12] than the triplet state of its xanthone analogue. While the latter compound decomposed instantaneously (< 10 min) upon irradiation ($\lambda = 366$ nm) in toluene,[13] **1** showed a detectable lifetime at $\lambda = 400$–700 nm. After 60 minutes approximately 35 % of the compound was degraded. In trifluorotoluene ($PhCF_3$) the stability was even higher. After 60 minutes, less than 10 % of the material was decomposed based on UV/Vis measurements (see the Supporting Information). The thioxanthone **1** therefore seemed well suited to catalyze photochemical reactions[14] in trifluorotoluene while employing a visible-light source.

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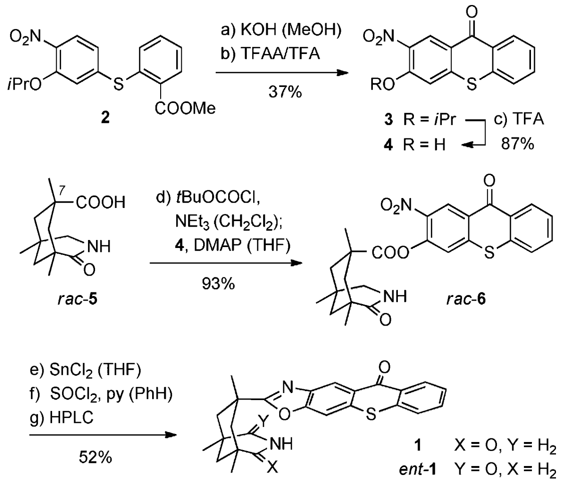
[**] This project was supported by the Deutsche Forschungsgemeinschaft (DFG) and by the Fonds der Chemischen Industrie. R.A. is the recipient of an Alexander von Humboldt research fellowship. We thank Olaf Ackermann and Marcus Wegmann for help with the HPLC analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201310997.



Scheme 1. Synthesis of **1**. Reaction conditions: a) KOH (10 equiv), MeOH, reflux, 5 h, 62%; b) TFA (24.3 equiv), TFAA (26.7 equiv), CH_2Cl_2, RT, 16 h, 60%; c) TFA, reflux, 3 d, 87%; d) *rac*-**5** (1.1 equiv), *t*BuOCOCl (1.1 equiv), NEt_3 (1.2 equiv), CH_2Cl_2, 0°C, 5 h; **4** (1.0 equiv), DMAP (0.1 equiv), THF, RT, 16 h, 93%; e) $SnCl_2$ (5.0 equiv), THF, reflux, 16 h; f) $SOCl_2$ (3.0 equiv), py (6.5 equiv), PhH, reflux, 6 h, 52% over two steps; g) ChiralPak AD-H (250×4.6 mm) *n*-hexane/*i*PrOH 50:50, 1 $\mathrm{mL\,min^{-1}}$, $t_R(\mathbf{1}) = 5.7$ min, $t_R(ent\text{-}\mathbf{1}) = 46.9$ min. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, TFAA = trifluoroacetic anhydride, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

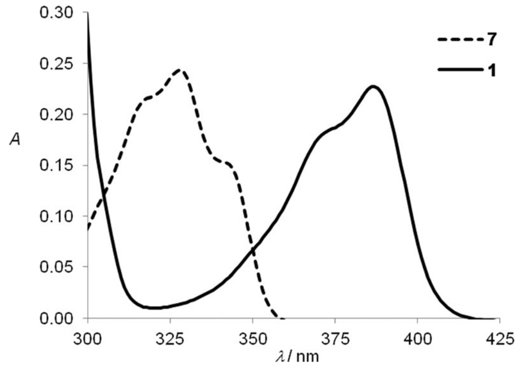
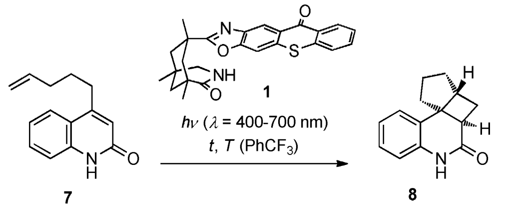


Figure 1. UV/Vis spectra of **1** ($c = 0.5$ mM) and **7** ($c = 0.5$ mM) in trifluorotoluene ($PhCF_3$).

The quinolone **7** was selected as a test substrate because it shows—compared to other quinolones—a relative long wavelength absorption, thus indicating that the energy of its triplet excited state might be lower than the triplet state energy of quinolone ($E_T = 276\ \mathrm{kJ\,mol^{-1}}$).[15] As expected from its spectral properties (Figure 1), the compound is readily converted into **8** upon irradiation at $\lambda = 300$ nm.[9b] With a visible-light source, however, there is no reaction to be observed after 60 minutes in trifluorotoluene at −25 °C (Table 1, entry 1). To our delight, addition of 10 mol% of **1** to the reaction mixture led, with all other parameters unchanged, to a clean intramolecular [2+2] photocycloaddition which generated **8** in 88% yield with 90% *ee* (entry 2). The reaction remained highly enantioselective even if performed at room temperature (entry 3), a feature which may eventually allow highly enantioselective reactions under ambient conditions by solar irradiation.[16] Since the catalyst is not completely stable in trifluorotoluene it was probed whether shorter reaction times lead to higher enantioselectivities, and it was indeed found to be the case (entry 4). Lowering the amount of catalyst led to a slightly increased reaction time and to a minimal decrease in enantioselectivity (entry 5). The substrate concentration influenced the time required for complete conversion but not the enantioselectivity (entries 6 and 7).

Table 1: Variation of reaction conditions for the enantioselective intramolecular [2+2] photocycloaddition of **7** catalyzed by **1**.



Entry[a]	*c* [mM]	equiv of **1**	*T* [°C]	*t* [min][b]	Yield [%][c]	*ee* [%][d]
1	2.5	–	−25	60	–	–
2	2.5	0.1	−25	60	88	90
3	2.5	0.1	RT	60	83	84
4	2.5	0.1	−25	30	86[e]	92
5	2.5	0.05	−25	75	90	87
6	1.0	0.1	−25	30	99	89
7	5.0	0.1	−25	75	86	91

[a] All reactions were conducted using a Rayonet RPR-100 reactor with 16 Osram L 8W/640 cool white lamps (Duran apparatus) as the irradiation source in deaerated trifluorotoluene. [b] Elapsed reaction time to achieve 100% conversion of the starting material. [c] Yield of isolated product after chromatographic purification. [d] The enantiomeric excess (*ee*) was calculated from the enantiomeric ratio, which was determined by HPLC analysis using a chiral stationary phase (see the Supporting Information). [e] 90% conversion.

Additional experiments showed that—as indicated by the UV/Vis studies—catalyst decomposition is not severe. After an irradiation time of 60 minutes (Table 1, entry 2), catalyst recovery was (85 ± 10)% and a clean ^{1}H NMR spectrum of the catalyst was obtained (see the Supporting Information). Moreover, since the employed visible-light source showed minimal emission in the UV range, we also used another set of lamps (RPR-4190 Å), which do not emit any UV light. Under conditions otherwise identical to those of entry 4 in Table 1, conversion was complete and **8** was obtained in 84% yield and with 96% *ee*. The catalyst recovery was also high in this experiment [(85 ± 10)%].

Given the success encountered in the enantioselective reaction of the test substrate **7**, related quinolones were prepared and subjected to the optimal reaction conditions (Table 1, entry 2: $c = 2.5$ mM, 10 mol% catalyst, 60 min irradiation time at −25 °C). The synthesis of the starting materials was straightforward (see the Supporting Information). Compounds with an all-carbon tether were prepared from commercially available 4-methylquinolone by deprotonation and subsequent alkylation.[17] Oxygen and nitrogen analogues were synthesized by nucleophilic substitution of 4-bromomethylquinolone[18] with the respective allylic alcohol or amine.

Irradiation experiments proceeded smoothly and delivered the expected tetracyclic products **9**–**14** in excellent yields

(79–97 %) and with high enantioselectivities (87–94 % *ee*; Figure 2). No other regio- or diastereoisomers were detectable. The products **11** and **13**, having a newly generated all-carbon bicyclo[3.2.0]heptane skeleton, showed the highest *ee* values, which even exceeded the *ee* value of the unsubstituted product **8** (Table 1). The enantioselectivity recorded for the heteroatom analogues **9**, **10**, **12**, and **14** were slightly lower. The time required for the complete conversion into **10** was four hours and it was 90 minutes for conversion into **12**. All other reactions went to completion after 60 minutes.

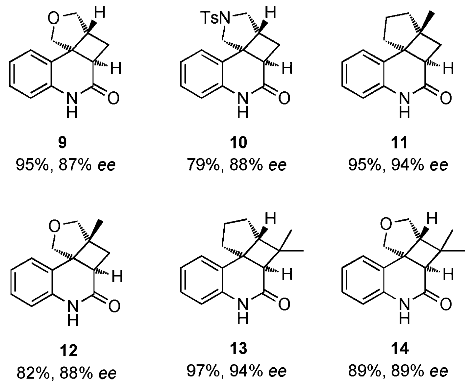
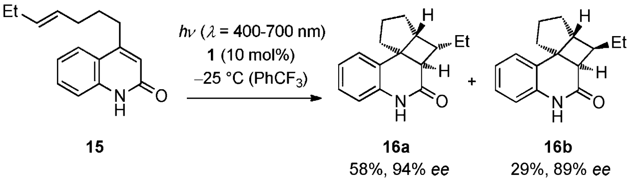

9 95%, 87% *ee*
10 79%, 88% *ee*
11 95%, 94% *ee*
12 82%, 88% *ee*
13 97%, 94% *ee*
14 89%, 89% *ee*

Figure 2. The products **9**–**14** of the enantioselective intramolecular [2+2] photocycloaddition of various quinolones catalyzed by **1**.

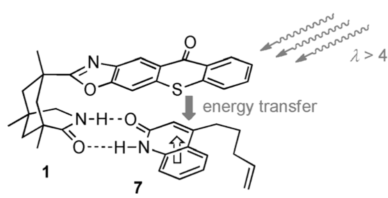
Regarding the olefin configuration at the reacting alkenyl chain, it was recognized in earlier studies that a non-stereospecific reaction course is typical for reactions proceeding via triplet intermediates.[19] Intermediate 1,4-diradicals exhibit a significantly long lifetime to allow free rotation before final ring closure.[20] In agreement with the postulated triplet-energy transfer by **1**, it was found that indeed (*E*)-4-(hept-4-enyl)quinolone (**15**) gave a mixture of two products (**16**), in which the respective *cis*-isomer **16a** prevailed (Scheme 2). The *trans*-isomer **16b**, which would be the expected product of a stereospecific reaction, was found to be the minor diastereoisomer. The enantioselectivity of the intramolecular [2+2] photocycloaddition was again excellent (94 % and 89 % *ee*).



15
16a 58%, 94% *ee*
16b 29%, 89% *ee*

Scheme 2. Intramolecular enantioselective [2+2] photocycloaddition of (*E*)-4-(hept-4-enyl)quinolone (**15**).

The hydrogen-bonding properties of the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton, to which the thioxanthone part of **1** is connected, have been established[21] and it appears safe to assume that a precoordination of quinolone substrates occurs, as depicted in Figure 3, to give the putative complex **1·7**. The thioxanthone acts as light-harvesting antenna, which transmits the energy of the absorbed photon to the quinolone, presumably by triplet-energy transfer.[22] Enantioface differentiation is provided by the planar thioxanthone so that attack at the quinolone double bond occurs with high selectivity. The deviation in enantioselectivity when comparing products **9**–**14** (Figure 2) does not necessarily reflect the binding properties of the individual substrates but may also be related to the rate of intramolecular addition (to a 1,4-diradical) versus dissociation of the complex **1·7**.[9c]



1
7

Figure 3. Mechanistic model for sensitization and enantioface differentiation in the complex **1·7**. The unshaded arrow indicates the approach of the tethered alkene onto the excited quinolone double bond.

In summary, the chiral thioxanthone **1** was synthesized, and was shown to act as an efficient sensititzer for enantioselective intramolecular [2+2] photocycloaddition reactions. To the best of our knowledge, **1** is the first chiral photocatalyst capable of processing visible light for a highly enantioselective photochemical reaction. Its relatively high triplet energy should enable other triplet-sensitized reactions to occur in an enantioselective fashion.

Received: December 19, 2013

Keywords: cycloaddition · enantioselectivity · hydrogen bonds · organocatalysis · photochemistry

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[1] a) G. Ciamician, P. Silber, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1928–1935; b) G. Büchi, I. M. Goldman, *J. Am. Chem. Soc.* **1957**, *79*, 4741–4748.

[2] a) E. Paternò, G. Chieffi, *Gazz. Chim. Ital.* **1909**, *39–1*, 341–361; b) G. Büchi, C. G. Inman, E. S. Lipinsky, *J. Am. Chem. Soc.* **1954**, *76*, 4327–4331.

[3] H.-D. Scharf, J. Fleischhauer, J. Aretz in *Methoden der Organischen Chemie (Houben-Weyl), 4th* ed., *Vol. IV/5a* (Ed.: E. Müller), Thieme, Stuttgart, **1975**, pp. 41–89.

[4] Z. Lu, T. P. Yoon, *Angew. Chem.* **2012**, *124*, 10475–10478; *Angew. Chem. Int. Ed.* **2012**, *51*, 10329–10332.

[5] General reviews on [2+2] photocycloaddition reactions: a) J. P. Hehn, C. Müller, T. Bach in *Handbook of Synthetic Photochemistry* (Eds.: A. Albini, M. Fagnoni), Wiley-VCH, Weinheim, **2009**, pp. 171–215; b) S. A. Fleming in *Molecular and Supramolecular Photochemistry, Vol. 12* (Eds.: A. G. Griesbeck, J. Mattay), Marcel Dekker, New York, **2005**, pp. 141–160; c) P. Margaretha in *Molecular and Supramolecular Photochemistry, Vol. 12* (Eds.: A. G. Griesbeck, J. Mattay), Marcel Dekker, New York, **2005**, pp. 211–237; d) J.-P. Pete in *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed. (Eds.: W. Horspool, F. Lenci), CRC, Boca Raton, **2004**, pp. 71/1–71/14; e) T. Bach, *Synthesis* **1998**, 683–703; f) J.-P. Pete, *Adv. Photochem.* **1996**, *21*, 135–216; g) J. Mattay, R. Conrads, R. Hoffmann in *Methoden der Organischen Chemie (Houben-Weyl) 4th* ed.,

Vol. E 21c (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 3085–3132; h) M. T. Crimmins, T. L. Reinhold, *Org. React.* **1993**, *44*, 297–588.

[6] Reviews: a) C. Yang, Y. Inoue, *Chem. Soc. Rev.* **2014**, DOI: 10.1039/c3cs60339c; b) C. Müller, T. Bach, *Aust. J. Chem.* **2008**, *61*, 557–564.

[7] For a different approach to enantioselective [2+2] photocycloaddition reactions, see: R. Brimioulle, T. Bach, *Science* **2013**, *342*, 840–843.

[8] S. L. Murov, I. Carmichael, G. L. Hug, *Handbook of Photochemistry*, 2nd ed., Dekker, New York, **1993**, p. 80, 91.

[9] a) C. Müller, A. Bauer, T. Bach, *Angew. Chem.* **2009**, *121*, 6767–6769; *Angew. Chem. Int. Ed.* **2009**, *48*, 6640–6642; b) C. Müller, M. M. Maturi, A. Bauer, M. C. Cuquerella, M. A. Miranda, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 16689–16697; c) M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.* **2013**, *19*, 7461–7472.

[10] A. B. Reitz, M. E. McDonnell, E. W. Baxter, E. E. Codd, W.-N. Wu, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1927–1930.

[11] X. Du, H. Liu, D.-M. Du, *Tetrahedron: Asymmetry* **2010**, *21*, 241–246.

[12] a) P. J. Wagner, B.-S. Park, *Org. Photochem.* **1991**, *11*, 227–3667; b) E. C. Lathioor, W. J. Leigh, *Photochem. Photobiol.* **2006**, *82*, 291–300.

[13] A. Bauer, Ph.D. thesis, TU München, **2006**.

[14] For thioxanthone-sensitized [2+2] photocycloaddition reactions, see: a) A. Padwa, T. J. Blacklock, *J. Am. Chem. Soc.* **1977**, *99*, 2345–2347; b) P. C. Wong, D. R. Arnold, *Can. J. Chem.* **1979**, *57*, 1037–1049; c) A. Padwa, T. J. Blacklock, R. Loza, R. Polniaszek, *J. Org. Chem.* **1980**, *45*, 2181–2189; d) A. Padwa, M. W. Wannmaker, *Tetrahedron Lett.* **1986**, *27*, 5817–5820.

[15] S. L. Murov, I. Carmichael, G. L. Hug, *Handbook of Photochemistry*, 2nd ed., Dekker, New York, **1993**, p. 82.

[16] Reviews: a) P. Esser, B. Pohlmann, H.-D. Scharf, *Angew. Chem.* **1994**, *106*, 2093–2108; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2009–2023; b) M. Oelgemöller, C. Jung, J. Mattay, *Pure Appl. Chem.* **2007**, *79*, 1939–1947; c) S. Protti, M. Fagnoni, *Photochem. Photobiol. Sci.* **2009**, *8*, 1499–1516; d) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527–532.

[17] a) O. Martin, E. de La Cuesta, C. Avendaño, *Tetrahedron* **1995**, *51*, 7547–7554; b) M. Dressel, T. Bach, *Org. Lett.* **2006**, *8*, 3145–3147; c) P. Selig, T. Bach, *J. Org. Chem.* **2006**, *71*, 5662–5673.

[18] R. G. Kalkhambkar, G. M. Kulkarni, C. M. Kamanavalli, N. Premkumar, S. M. B. Asdaq, C. M. Sun, *Eur. J. Med. Chem.* **2008**, *43*, 2178–2188.

[19] a) D. Becker, M. Nagler, S. Hirsh, J. Ramun, *J. Chem. Soc. Chem. Commun.* **1983**, 371–373; b) D. Becker, M. Nagler, Y. Sahali, N. Haddad, *J. Org. Chem.* **1991**, *56*, 4537–4543; c) D. Becker, N. Klimovich, *Tetrahedron Lett.* **1994**, *35*, 261–264.

[20] D. I. Schuster, G. Lem, N. A. Kaprinidis, *Chem. Rev.* **1993**, *93*, 3–22.

[21] A. Bakowski, M. Dressel, A. Bauer, T. Bach, *Org. Biomol. Chem.* **2011**, *9*, 3516–3529.

[22] D. L. Dexter, *J. Chem. Phys.* **1953**, *21*, 836–850.