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Light-Driven Enantioselective Organocatalysis**

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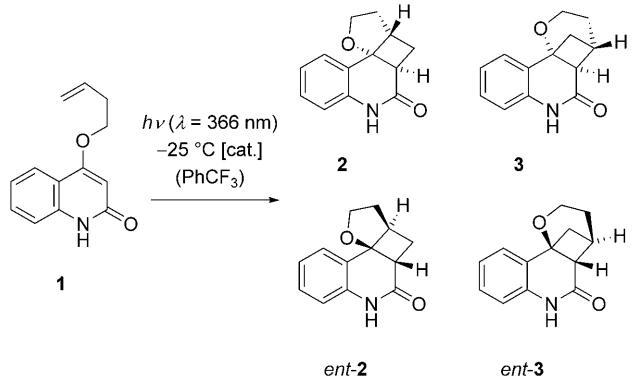
In recent years, organocatalysis has emerged as an important area of modern catalysis that complements metal catalysis and enzyme catalysis.[1] Many chiral compounds that could not be prepared previously in enantiomerically pure form by other transformations, or which were only obtained in tedious reaction sequences, were made accessible by organocatalytic reactions.[2] Nonetheless, there are still many product classes that are not available by conventional enantioselective organocatalysis. Any reaction pathway requiring photochemical but not thermal activation is inherently impossible to be catalyzed by a classical organocatalyst unless the process of photochemical activation and catalysis are separated.[3] Processes in which light energy serves as direct driving force for enantioselective bond formation require the design of chiral organocatalysts to harvest light and allow sensitization of the substrate by energy or electron transfer.[4,5] After initial success in this area employing a catalytic photoinduced electron transfer (up to 70% *ee* with 30 mol% catalyst),[6] herein we present a chiral organocatalyst that combines a significant rate acceleration by triplet energy transfer[7] with high enantioselectivities. In the studied test reaction (Scheme 1), a yield of 90% and an enantioselectivity of 92% *ee* were achieved with only 10 mol% of this catalyst.



Scheme 1. Intramolecular [2+2] photocycloaddition of prochiral 4-(3′-butenyloxy)quinolone **1** to the products **2**/*ent*-**2** and **3**/*ent*-**3**.

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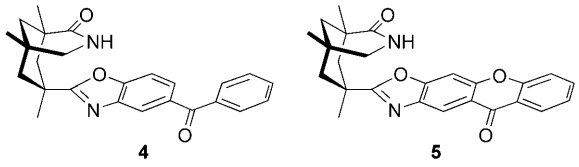
The intramolecular [2+2] photocycloaddition of quinolone **1**, first described by Kaneko et al., leads to two regioisomeric products: the predominant straight product **2**, and the crossed product **3**.[8] This particular transformation was selected as test reaction, because it delivers a cycloaddition product by a rapid five-membered ring closure,[9] and because it had already been shown by Krische et al.[10] that a sensitization of this reaction is possible by a chiral benzophenone (19% *ee* with 25 mol% catalyst). The latter result provided hope that a catalytic reaction course might be feasible with the benzophenone **4** described earlier.[6] The



solvent, trifluorotoluene,[11] and the irradiation conditions ($\lambda = 366$ nm) were adapted to achieve maximum stability and selective excitation of the sensitizer. Indeed, compound **1** shows only a weak UV absorption at wavelengths of more than 350 nm. Consequently, the irradiation with a light source that emits at 366 nm (see Supporting Information), resulted only in a low conversion after one hour at ambient temperature (Table 1, entry 1).

Benzophenone **4** was then used as catalyst, but unfortunately, it performed less successfully than expected in the attempted enantioselective catalysis experiments. A rate acceleration of the reaction was observed, but the enantioselectivities remained low. The best result was achieved in trifluorotoluene at −25 °C (Table 1, entry 2). At lower temperatures (using toluene as the solvent), no conversion took place. As the relatively low triplet energy and the comparably short wavelength absorption of benzophenone **4** were probably responsible for the disappointing results, the synthesis of xanthone **5** as a potentially more active catalyst was attempted. The synthesis required careful optimization, and commenced with the commercially available fluorophenol **6** (Scheme 2). After protection of the hydroxy group, nucleophilic substitution with the sodium salt **7** of methyl salicylate produced biarylether **8**. Upon saponification of the ester group, the xanthone ring was formed by an intramolecular Friedel–Crafts acylation.[12] Product **9** was obtained as the free phenol after cleavage of the isopropyl protecting group. Esterification with the mixed anhydride *rac*-**10** (see the Supporting Information)[13,14] produced intermediate product *rac*-**11**. Subsequent reduction of the nitro group was accompanied by an ester aminolysis,[15] and the resulting *ortho*-hydroxyanilide could be cyclized smoothly to the required

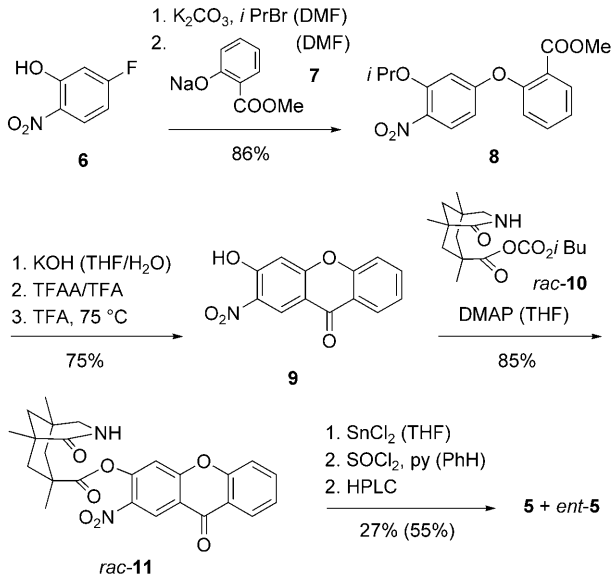
Table 1: Intramolecular [2+2] photocycloaddition of substrate **1** to form products **2** and **3** (Scheme 1): Influence of catalysts on conversion and enantioselectivity.

Entry	Catalyst	Mol %[a]	*t* [h]	Conv. [%][b]	Yield [%][b]	r.r.[c]	*ee* (**2**) [%][d]	*ee* (**3**) [%][d]
1	–	–	1	14	–	86/14	–	–
2	**4**	10	1	57	90	75/25	39	17
3	**5**	10	1	64	90	78/22	92	90
4	**5**	10	2	78	89	77/23	91	91
5	**5**	10	4	90	55	>99/1	91	–
6	**5**	5	1	50	95	78/22	90	n.d.[e]
7	**5**	20	1	73	78	79/21	94	94
8	xanthone	10	1	39	77	79/21	–	–

[a] Reactions were carried out under argon in deaerated trifluorotoluene as solvent at −25 °C (irradiation at 366 nm) and with a substrate concentration of 5 mM (see Supporting Information). [b] The conversion and yield were determined gravimetrically after separation of substrate (**1**) and products (**2**,**3**). Conversion and yield are calculated based on recovered starting material. [c] The **2**/**3** regiomeric ratio (r.r.) was determined by HPLC. [d] The enantiomeric excess (*ee*) was determined by HPLC. [e] The *ee* value could not be determined in this case.

69% yield (89% based on recovered starting material). Comparison of the catalysis results (Table 1, entries 3–7) with the background reaction (Table 1, entry 1) reveals that the success of the catalyst is largely due to its ability to significantly reduce any unsensitized photocycloaddition—an effect of its UV absorption properties (Figure 1).

As a consequence, the enantioselectivity depends only marginally on the catalyst concentration (Table 1, entries 6, 7). It decreased slightly with 5 mol% catalyst (Table 1, entry 6), and increased to



Scheme 2. Synthesis of the xanthone sensitizer **5** starting with commercially available fluorophenol **6** (see also Supporting Information). DMAP = 4-dimethylaminopyridine, py = pyridine, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

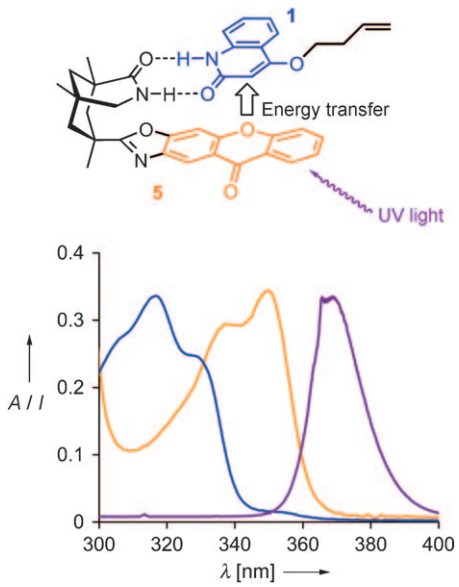


Figure 1. Mode of action of catalyst **5** illustrated by the normalized absorption spectra of substrate **1** (——) and xanthone **5** (——), and by the normalized emission spectrum of the irradiation source (——).

benzoxazole. A separation of enantiomers from the racemic mixture *rac*-**5** was possible by semipreparative chiral HPLC, so that the desired xanthone **5** and its enantiomer *ent*-**5** were available for catalysis experiments.

Xanthone catalyst **5** shows a relatively high absorption coefficient at wavelengths $\lambda \geq 350$ nm ($\varepsilon_{350} = 9200$ in $PhCF_3$; Figure 1). The chirality turnover achieved with 10 mol% **5** was extraordinarily high, with enantioselectivities reaching or exceeding 90% *ee* for both products **2** and **3** after one hour of irradiation at −25 °C (Table 1, entry 3). Conversion increased with increasing reaction time (Table 1, entries 4, 5) but isolation became troublesome owing to decomposition of the sensitizer.

The best compromise from a preparative perspective was to stop the reaction with 10 mol% catalyst after 2 h and 78% conversion. Under these conditions, products were isolated in 94% *ee* with 20 mol% of catalyst (Table 1, entry 7). The regioisomeric product **3** turned out to be unstable under the irradiation conditions, and thus isolable quantities were not detected after four hours of irradiation (Table 1, entry 5). The comparison of **5** with the parent compound xanthone (Table 1, entry 8) underscores the point that intramolecular sensitization by triplet energy transfer[7] within the substrate–catalyst complex **1**·**5** is more efficient than intermolecular sensitization. As depicted in Figure 1, the catalyst **5** achieves a selective excitation of substrate **1** and therefore fulfills perfectly the requirements of a chiral triplet sensitizer for enantioselective photoreactions:

1. The activation process works only selectively if there is little or no spectral overlap between substrate and catalyst in a wavelength region in which an excitation of the catalyst is possible with a given light source. For catalyst **5**,

this optical window appears ideally positioned (Figure 1) to avoid direct excitation of substrate **1**.

2. The triplet energy of the sensitizer must be significantly higher than the triplet energy of the substrate to allow rapid energy transfer even at low temperature. Based on the estimated[16] triplet energies for quinolone **1** ($E_T \approx 280\ kJ\,mol^{-1}$) and xanthone **5** ($E_T \approx 310\ kJ\,mol^{-1}$), this criterion is fulfilled for both components of complex **1·5**.
3. The substrate–catalyst complex must form effectively to ensure that the sensitization in this complex is faster than intermolecular sensitization. In the example presented herein, complex formation was achieved by hydrogen bonding, employing a motif previously established in a stoichiometrically applied template.[13,17]
4. An effective differentiation of enantiotopic faces or groups must be guaranteed by a chiral control element in the catalyst. In addition, substrate dissociation must be slow relative to the projected reaction, so that after sensitization, the excited substrate still encounters the steric bias exerted by the control element.

Although many solutions are conceivable to meet the requirements listed above, we believe that the catalyst we have constructed can serve as a prototype for further developments in the field. Its application to synthetically relevant transformations of quinolones is currently under investigation.

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