Organophotocatalysis

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Enantioselective Organo-Photocatalysis Mediated by Atropisomeric Thiourea Derivatives**

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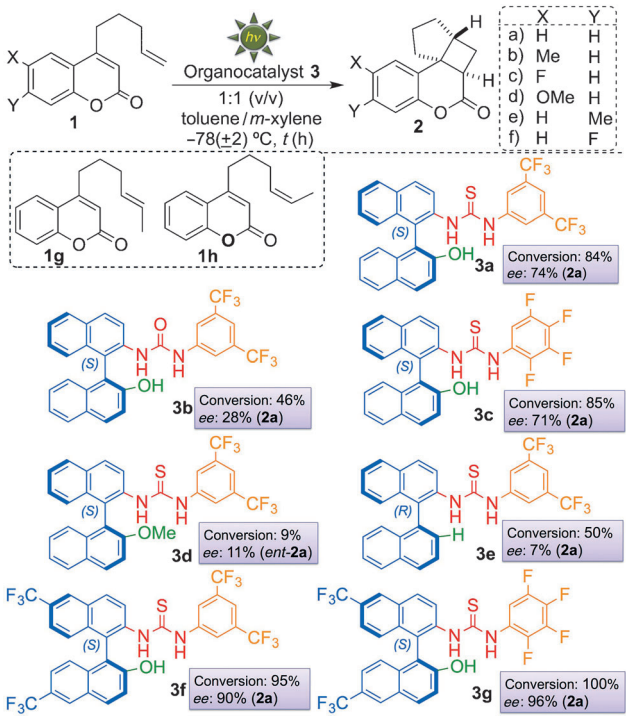
Abstract: *Can photocatalysis be performed without electron or energy transfer? To address this, organo-photocatalysts that are based on atropisomeric thioureas and display lower excited-state energies than the reactive substrates have been developed. These photocatalysts were found to be efficient in promoting the [2+2] photocycloaddition of 4-alkenyl-substituted coumarins, which led to the corresponding products with high enantioselectivity (77–96 % ee) at low catalyst loading (1–10 mol %). The photocatalytic cycle proceeds by energy sharing via the formation of both static and dynamic complexes (exciplex formation), which is aided by hydrogen bonding.*

Light-induced processes in nature have served as an inspiration to chemists for the design and development of model systems to perform chemical or physical processes.[1] Recently, energy-transfer[2] and electron-transfer[3] processes have been at the forefront of the development of catalytic organic photoreactions.[4] For successful energy/electron transfer, it is critical to match the excited-state energies (for energy transfer) or the redox potential (for photoredox catalysis) of the sensitizer with that of the reactive substrate.[5] To develop an alternative strategy that does not depend on energy/electron transfer to initiate the photoreactions and to employ catalysts with excited-state energies that are lower than those of the reactive substrate(s), our approach was to enable complex formation (static/dynamic complexes or exciplexes) between the organocatalyst and the reactive substrate. We believed that such an approach would allow us to develop catalysts that could be fine-tuned both electronically and sterically to manipulate catalyst–substrate interactions, as the exciplex formation that leads to stereocontrolled photoreactions has literature precedence.[6] More importantly, it would enable us to control the excited-state interactions using well-established stereoelectronic effects.

During our initial screening, we identified atropisomeric binaphthyl-derived thioureas[7] as potential catalysts for promoting photoreactions.[8] As the synthesis of thioureas is modular, it will enable us to fine-tune the electronic and steric properties of the catalysts, thereby influencing non-bonding interactions, which will have an impact on the excited-state reactivity and the stereoselectivity of the photoreaction of interest.[7] Furthermore, thiourea catalysts are robust, display excellent stability, and do not require any special handling (e.g., inert conditions) when they are employed for photoreactions.[9]

To evaluate the atropisomeric thiourea derivatives **3** as organo-photocatalysts, we selected an established photoreaction that involves the intramolecular [2+2] photocycloaddition of 4-alkenyl-substituted coumarins[10] **1a–d** leading to the cyclized photoproduct **2**, which bears a quaternary chiral center, as the model system (Scheme 1). The [2+2] photo-



Scheme 1. Enantioselective intramolecular [2+2] photocycloaddition of coumarin **1** promoted by thioureas **3a–g**.

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cycloaddition of coumarins with alkenes is well established and can occur either via a singlet excited state or via a triplet excited state.[10] Pioneering studies by Lewis and co-workers[10b] in the early 1980s established that photoreactions of coumarins can be fine-tuned by the addition of Lewis acids that interact with the carbonyl functional group, which alters the properties of the excited state. Based on this precedence, Bach and co-workers[10c,d] have recently developed an enantioselective [2+2] photocycloaddition of 4-alkenylcoumarin derivatives that is mediated by a chiral Lewis acid. Furthermore, an electron-transfer-mediated cycloaddition reaction was recently reported by Griesbeck, Schmalz, and co-workers.[11] Our method provides complementarity to the existing strategies by controlling the excited-state reactivity through static/dynamic complex formation (exciplex formation) and circumvents the bottleneck of employing catalysts that have higher excited-state energies than the reactive substrates, thus opening up new avenues for the development of novel organo-photocatalysts.

The intramolecular [2+2] photocycloaddition of coumarin **1** was performed with various chiral thiourea derivatives **3a**–**3g** at different temperatures and in various solvents using light with a wavelength of approximately 350 nm.[12] The reaction was followed by ^{1}H NMR spectroscopy and/or by gas chromatography. Photoproduct **2** was characterized by NMR spectroscopy, high-resolution mass spectrometry (HRMS), and single-crystal X-ray diffraction (XRD). Analysis of the reaction mixture by GC and/or HPLC on a chiral stationary phase gave the enantiomeric excess (*ee* values) of **2**. To evaluate the thiourea organo-photocatalysts, we used the [2+2] photocycloaddition of **1a** as the model system, which led to the corresponding photoproduct **2a** (Scheme 1), and employed catalyst **3a**, as this catalyst could be readily prepared in one step from commercially available, optically pure 2-amino-2′-hydroxy-1,1′-binaphthalene. The interaction between **3a** and **1a** was reflected in the thermodynamic binding constant (K_d) value of $84 \pm 15\,\text{M}^{-1}$ (in methylcyclohexane (MCH) as the solvent). The absolute configuration of **2a** was determined by single-crystal XRD,[10c] and the product was found to be the (3*aR*,4*aR*,10*bS*) enantiomer. Based on solvent screening studies,[12] we identified a 1:1 toluene/xylene mixture as the best solvent with catalyst **3a** as we observed excellent conversion and mass balance, and the photoproduct was obtained with high enantioselectivity (84% conversion; 74% *ee*; Scheme 1).

To understand the interaction(s) between the catalyst and the substrate as well as to improve the enantioselectivity, we systematically varied the functional groups of catalyst **3**. We 1) compared the thiourea with a urea functional group (**3a** and **3b**); 2) varied the electron-withdrawing substituent that is attached to the thiourea unit (**3a**/**3c** vs. **3f**/**3g**); and 3) varied the functional groups on the binaphthyl unit (**3a**, **3d**, and **3e**). With thiourea catalyst **3a**, photoproduct **2** was obtained with 74% *ee* and 84% conversion (**1a**/**2a** = 11:89). On the other hand, the corresponding urea catalyst **3b** gave **2** with 28% *ee* and 46% conversion (**1a**/**2a** = 50:50). The precipitous drop in the *ee* value (from 74% *ee* to 28% *ee*) in **2a** as well as in the conversion (from 84% to 46%) was quite striking. It is important to note that in the presence of either the urea or thiourea catalyst, the desired product was formed with higher conversion than in the control reaction in the absence of the catalyst (9% conversion with racemic photoproducts). A comparison of the results with catalysts **3a** and **3b** clearly revealed the importance of the thiourea moiety in enhancing both the reactivity and the selectivity of the photocycloaddition process. We then varied the electron-withdrawing groups (EWGs) on the aryl ring that is attached to the nitrogen atom. The reactions with catalysts **3a**, which bears 3,5-trifluoromethyl substituents on the phenyl ring, and **3c**, which entails a tetrafluoro-substituted phenyl ring, indicated that both electron-withdrawing substituents were equally effective in promoting the [2+2] photocycloaddition of **1a** and led to the photoproduct with similar enantioselectivities (74% *ee* with **3a** and 71% *ee* with **3c**), conversion (84% for **3a** and 85% for **3c**), and mass balance.[12]

We then proceeded to systematically change the functional group(s) at the 2′-position of the binaphthyl unit to evaluate the role of hydrogen bonding in controlling the enantioselectivity of the photoreaction of **1a** with the binaphthyl-based thiourea catalyst. Photoproduct **2a** was obtained with 11% *ee* with catalyst **3d** (OMe substituent at the 2′-position; with enhancement of the antipode of the photoproduct, *ent*-**2a**) and 7% *ee* with catalyst **3e** (hydrogen substituent at the 2′-position), whereas catalyst **3a** gave the desired product in 74% *ee* (Scheme 1). It is likely that the methoxy substituent orients the substrate **1a** in a geometry that enhances the formation of the optical antipode of the photoproduct. As hydrogen-bonding interactions were established to be crucial, we believed that installing electron-withdrawing CF_3 groups at the 6- and 6′-positions of the binaphthyl backbone (**3f** and **3g**) would further enhance the enantioselectivity of the [2 + 2] photocycloaddition. As expected, both catalysts gave the photoproduct with high enantioselectivity (90% *ee* for **3f** and 96% *ee* for **3g**; Scheme 1). It was clear that the electron-withdrawing substituents on the *N*-aryl ring and in the 6 and 6′-positions of the binaphthyl backbone not only led to an increase in conversion (84% for **3a**, 95% for **3f,** and quantitative conversion for **3g**), but also to an enhanced enantioselectivity (from 74% *ee* for **3a** to 90% *ee* for **3f** and 96% *ee* for **3g**; Scheme 1).[12]

Having established the effectiveness of the thiourea derivatives in the intramolecular [2+2] photocycloaddition of **1a**, we evaluated the catalytic efficiency by conducting the phototransformation with different amounts of **3g**, which is the catalyst that gave the photoproduct with the highest *ee* value (Table 1). Initially, we conducted control experiments to ascertain the level of conversion for different irradiation times in the absence of the catalyst (Table 1). The data from these experiments suggest that there was a reasonable amount of background reactions at longer irradiation times (4 h; Table 1, entry 1). For the catalyzed reactions, reducing the catalyst loading from 100 to 30 to 10 mol% had a minimal impact on the enantioselectivity (94–96% *ee*; entries 2–4) of the photoaddition product, and the reaction was complete in 30 minutes. Remarkably, at 1 mol% of catalyst **3g**, the photoproduct was obtained with 77% *ee* after 30 minutes of irradiation (entry 7). The *ee* values slightly decreased on prolonged irradiation with 1 mol% of catalyst

Table 1: Enantioselective intramolecular [2+2] photocycloaddition of **1a** catalyzed by thiourea **3g**.[a]

Entry	**3g** [mol%]	*t* [h]	**1/2**[b]	*ee* of **2a** [%][b]
1	–	4	88:12	racemic
2	100	0.5[c]	0:100	96
3	30	0.5	0:100	94
4	10	0.5	0:100 (77)[d]	94 (92)[d]
5	5	0.5	41:59	89
6	5	1	07:93	88
7	1	0.5	64:36	77
8	1	1	52:48	75
9	1	2	30:70	74
10	1	4	17:83	69

[a] The samples were deaerated by N_2 bubbling for 8–10 minutes before irradiation. All reactions were conducted in a 1:1 toluene/*m*-xylene mixture at −78(±2) °C. [b] Determined by GC analysis on a chiral stationary phase. [c] Similar *ee* values and conversions were obtained after irradiation for two or three hours (error: ±3%). [d] Large-scale reaction (2 h), yield of isolated product: 77%, quantitative conversion.

3g (entries 8–10), which we believe is a reflection of competing uncatalyzed background reactions and/or product inhibition of the catalyst at very high conversions.

To investigate the generality of this thiourea-catalyzed enantioselective photocycloaddition, we evaluated different coumarin derivatives **1b**–**1d** with various substituents at the 6-position. The substituent at the 6-position of coumarin was varied from Me (**1b**) to F (**1c**) and to OMe (**1d**). High enantioselectivities of 88% and 90% *ee* were observed for the photoproduct with **1b** and **1c**, respectively.[12] Coumarin **1d** was specifically investigated to disrupt the hydrogen bonding between the catalyst and the substrate. As expected, the methoxy substituent in **1d** likely disrupts the hydrogen-bonding interaction between the substrate and the catalyst, which led to a low *ee* value of 16% for the photoproduct **2d**.[12] We also evaluated 7-substituted coumarins **1e** and **1f** and obtained the corresponding products with quantitative conversion and *ee* values of 92% and 90%, respectively with 10 mol% of catalyst **3g**. To ascertain the reactive spin state(s) of **1a** that are present during organo-photocatalysis by **3g**, the reaction was carried out under various atmospheres. The reaction was found to be very efficient under N_2 atmosphere in the presence of 10 mol% of catalyst, as **1a** was quantitatively converted into the photoproduct after irradiation for 30 minutes.[12] Under O_2 atmosphere (O_2 acts as a triplet quencher), the conversion was low (**1a**/**2a** = 88:12), whereas the conversion was moderate under aerated conditions (**1a**/**2a** = 47:53) after irradiation for two hours and with 10 mol% of catalyst **3g**.[12]

Detailed photophysical studies were performed (using catalyst **3a** and substrate **1a** as a representative example) to decipher the photocatalytic process and to determine 1) the type of interaction between the catalyst and the substrate in the ground state and/or the excited state; 2) the nature of the excited state; and 3) the excited-state kinetic and energetic aspects of catalyst and substrate. UV/Vis spectra revealed that the catalyst **3a** interacted with **1a**, which led to a bathochromic shift of the absorbance of the **3a**–**1a** mixture compared to the absorbance of catalyst **3a** on its own and substrate **1a** (Figure 1A). Steady-state fluorescence spectra at 23 °C showed a featureless emission that was centered at approximately 400 nm for catalyst **3a** with a singlet excited-state energy of 77 kcal mol^{-1} (Figure 1C, bottom), whereas a weak

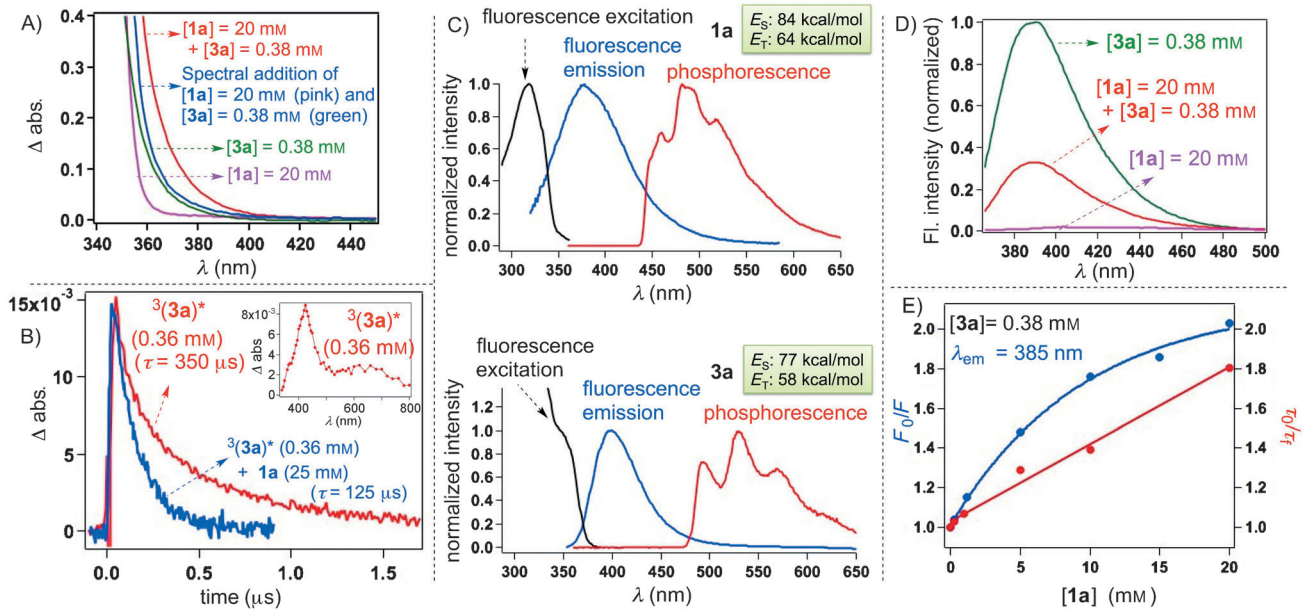

Figure 1. A) UV/Vis absorption spectra in methylcyclohexane (MCH). B) Transient absorption decay traces of ^{3}(**3a**)* monitored at 425 nm after pulsed laser excitation (355 nm, 5 ns) and transient absorption spectrum of **3a** in deoxygenated MCH (inset). C) Fluorescence excitation and emission spectra of **1a** (top) and **3a** (bottom) in toluene at room temperature and phosphorescence spectra in toluene glass at 77 K. D) Fluorescence of **3a** in the absence and presence of **1a** in MCH at room temperature. E) Stern–Volmer plot of **3a** showing the fluorescence intensity (blue) and fluorescence lifetime (red) in the presence of different concentrations of **1a**.

emission centered at approximately 380 nm was observed for **1a** with a singlet excited-state energy of 84 kcal mol^{-1} (Figure 1C, top). This shows that singlet energy transfer from catalyst **3a** to substrate **1a** is energetically unfavorable (the catalyst absorbs light because of its lower excited-state energy). Triplet energies were ascertained from the phosphorescence spectra at 77 K (Figure 1C) and were found to be 64 kcal mol^{-1} and 58 kcal mol^{-1} for **1a** and **3a**, respectively, indicating that a triplet–triplet energy transfer from the catalyst to the substrate is also unlikely.

Fluorescence quenching experiments were performed to investigate the nature of the catalyst–substrate interaction. The fluorescence of catalyst **3a** was quenched efficiently by substrate **1a** (Figure 1D). To elucidate the nature of the quenching mechanism, a Stern–Volmer analysis of the fluorescence signal of **3a** was performed under steady-state conditions with **1a** as the quencher (Figure 1E). A nonlinear response was observed under steady-state conditions, whereas a linear response was observed with lifetime measurements, which indicates that both static and dynamic quenching mechanisms are operating in our system. To examine whether the triplet excited state of the catalyst was also quenched by **1a**, the triplet–triplet absorption spectrum of **3a** was recorded (Figure 1B, inset). The transient absorption was assigned to the triplet state of **3a** based on similarities with previously published spectra of the triplet state of naphthalene.[13] The transient decay kinetic profile of the **3a** triplet [^{3}(**3a**)*] revealed a decreased lifetime of **3a** in the presence of **1a**, which again points to a dynamic mechanism (Figure 1B).

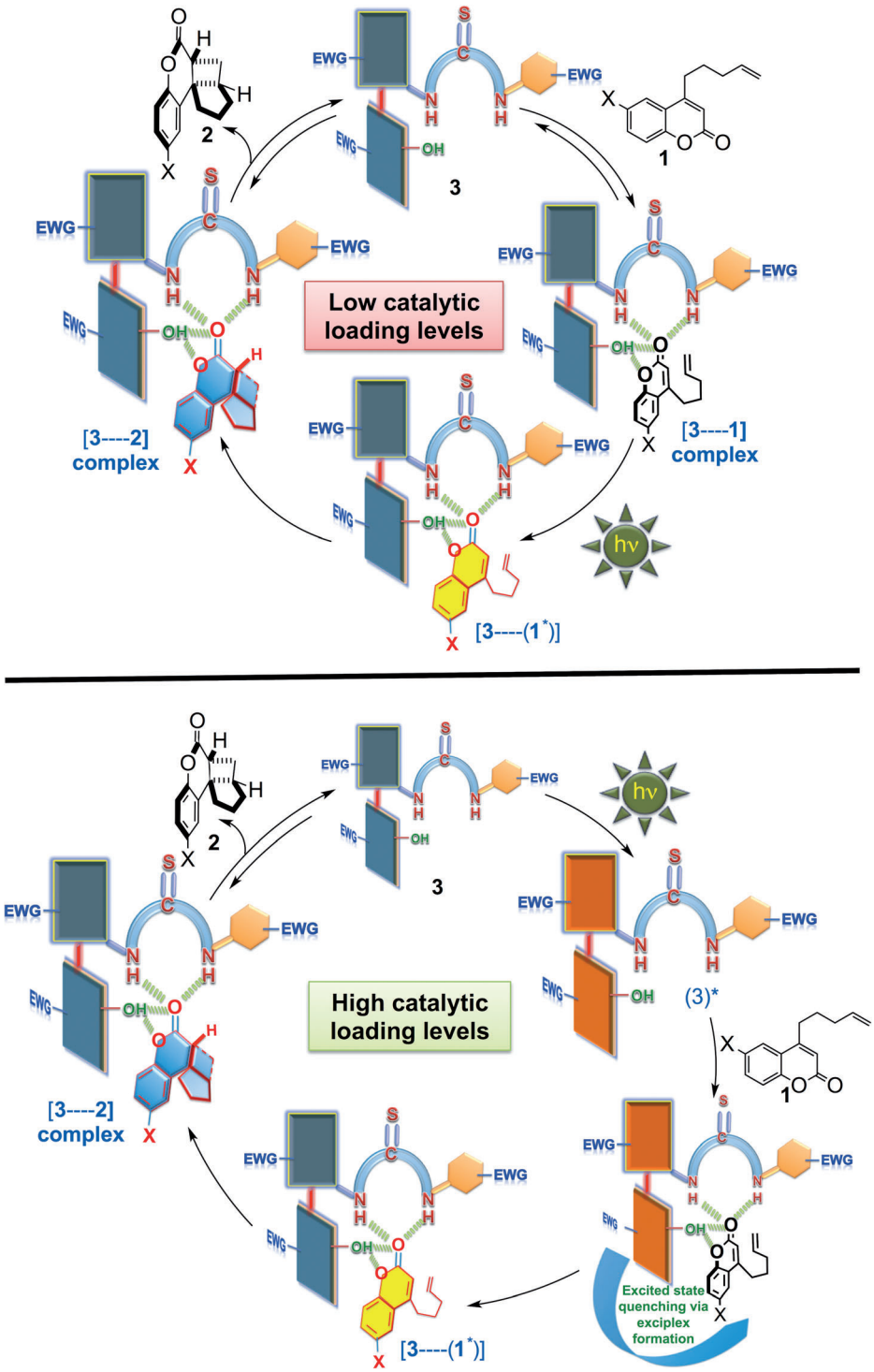

Figure 2. Enantioselective organo-photocatalysis with atropisomeric thiourea catalysts.

Based on our results with substrate **3a**, we propose a preliminary catalytic cycle (Figure 2) for the enantioselective organo-photocatalysis that involves hydrogen-bonding interactions between catalyst **3** and coumarin substrate **1**. The light-absorbing species in the system depends on the catalyst loading and is dictated by the absorptivity of the catalyst–substrate complex relative to the absorptivity of the catalyst. At high concentrations of the substrate (i.e., at low catalyst loading), the catalyst–substrate complex [**3a**–**1a**], which displays a bathochromic shift in its absorption spectrum, is excited efficiently. This excited complex reacts to form the photoproduct (Figure 2, top). At low concentrations of the substrate (i.e., at high catalyst loading), the catalyst absorbs light because of the higher optical density of **3** compared to

the catalyst–substrate complex [**3a**–**1a**].[12] The excited catalyst **3*** is efficiently quenched by substrate **1**, which leads to the formation of an exciplex with sharing of the excited-state energy (Figure 2, bottom). This exciplex formation subsequently results in the formation of the photoproduct. Whereas the reaction is promoted by the formation of static and dynamic complexes, the stereodifferentiation arises from the atropisomeric binaphthyl motif, which determines the enantiomeric excess of the photoproduct through the ability of substrate and catalyst to interact effectively through hydrogen bonding. The organo-photocatalytic transformation of **1a** with catalyst **3g** was more efficient under nitrogen atmosphere than under oxygen atmosphere, which suggests the involvement of a highly reactive triplet excited state of **1**. As there was a noticeable decrease in conversion in the presence of oxygen, it is likely that the reaction pathway involves a singlet excited state and/or partial quenching of the triplet excited state (because of inefficient quenching by oxygen). Control studies[12] with substrates **1g** and **1h** (Scheme 1) revealed *cis*/*trans* isomerization of the alkene double bond during the course of the reaction that is catalyzed by **3a**, albeit with low efficiency.[10c,12] This likely has its origin in the involvement of a triplet 1,4-biradical that is formed during the catalytic process and that can either cyclize to form the photoproduct or revert to the starting material, thus scrambling the *cis*/*trans* alkene geometry in **1g** and **1h**.[12] At low catalyst loading (1 mol%), the product likely binds to the catalyst (product inhibition) at high conversions. Furthermore, background reactions are also likely to compete with the enantioselective catalytic transformation at low catalyst loading (Table 1). These two factors are reflected in the slight decrease in enantioselectivity for higher conversions at very low catalyst loading (1 mol%). At a catalyst loading of 10 mol%, the catalyst turnover was efficient, which allows for high *ee* values and quantitative conversion into the desired photoproduct.

Our study has clearly established that binaphthyl-based thiourea derivatives are motifs that efficiently absorb light and promote photochemical transformations with good enantiocontrol. The ability to fine-tune organocatalysts both sterically and electronically to influence photochemical reactions has the potential to foster new opportunities in the area of asymmetric photoreactions.[14] The manipulation of excited-state reactivity through the formation of static and dynamic complexes (exciplex formation) presents an opportunity to sidestep the criteria of having photocatalysts or sensitizers with higher excited-state energies than the reactive substrates that undergo the desired transformation, which thus opens up new avenues to develop novel organo-photocatalysts and synthesize products with structural features that are unique to photoreactions.

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