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Evaluating Thiourea Architecture for Intramolecular [2+2] Photocycloaddition of 4-Alkenylcoumarins

Nandini Vallavoju,[a] Sermadurai Selvakumar,[a] Steffen Jockusch,[b]
Manoj Thathamkulam Prabhakaran,[a] Mukund P. Sibi,[a,*]
and Jayaraman Sivaguru[a,*]

[a] Department of Chemistry and Biochemistry, North Dakota State University, Fargo, ND 58108-6040, USA
Fax: (+1)-701-231-8831; phone: (+1)-701-205-8338; e-mail: mukund.sibi@ndsu.edu or sivaguru.jayaraman@ndsu.edu
[b] Department of Chemistry, Columbia University, New York, NY 10027, USA

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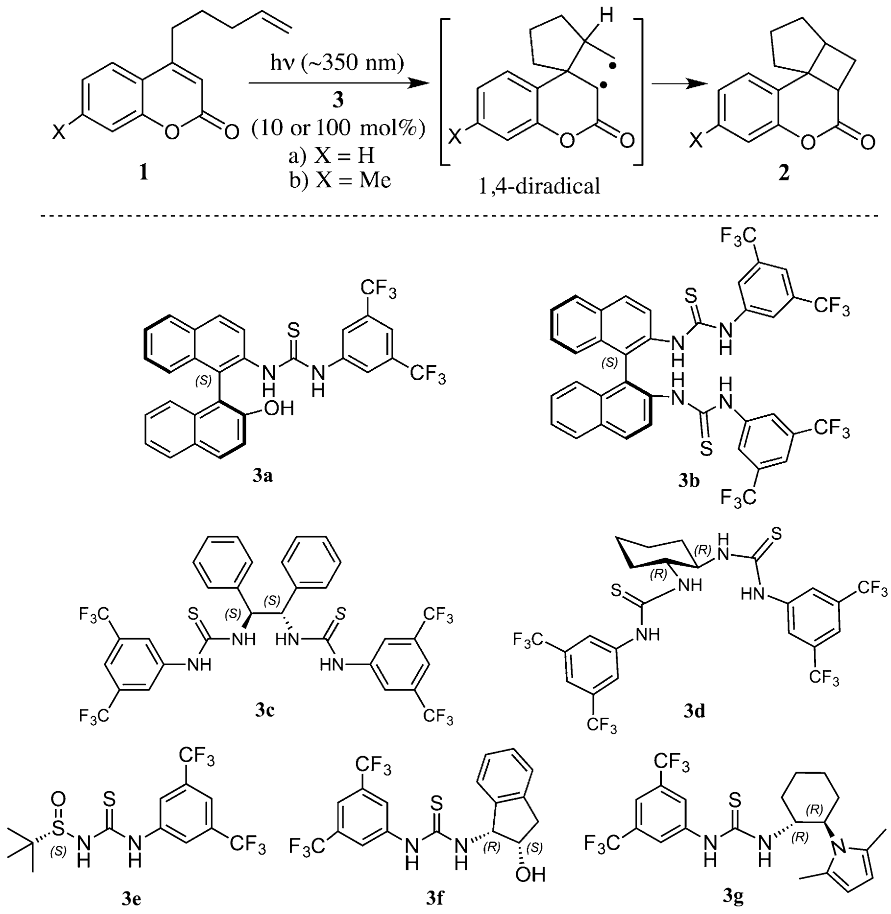
Abstract: The efficiency of [2+2] photocycloadditions of 4-alkenylcoumarins was evaluated with various thiourea skeletons to develop thiourea-based catalysts for promoting photochemical reactions. Our results indicate that the excited state chemistry is dependent on the nature of the thiourea catalyst employed to activate the photoactive substrate.

Keywords: asymmetric photoreactions; hydrogen bonding photocatalysis; organophotocatalysis; photochirogenesis; thiourea photocatalysis

Photochemical transformations are an important class of organic reactions that are often known to generate products with unique stereochemistry.[1] For this reason, chemists have developed strategies that are readily applied in organic synthesis.[2] In recent years, there has been tremendous impetus towards developing enantioselective syntheses of complex strained compounds by light initiated reactions.[1c,2i] In that regard three different catalytic strategies have garnered attention, as they are effective in controlling chemical transformations initiated by light. The first strategy involves photoredox chemistry[3] where a light absorbing sensitizer performs a one electron oxidation or reduction of the reactive substrate leading to a radical anion or a radical cation. As these reactive species are in the ground state, their higher potential enables them to react efficiently to form products. The second strategy involves an energy transfer mechanism[2h,4] where the excited state energy from a light absorbing sensitizer is transferred to the substrate, producing a singlet or a triplet excited state that reacts to form the product. This strategy requires the excited state energy of the sensitizer to be higher than that of the reactive substrate. The third strategy involves an energy sharing mechanism where, upon light excitation, the sensitizer/catalyst and reactant complex (static/dynamic complex) undergo a phototransformation to form the product(s).[5]

We have embraced the energy sharing strategy and have utilized thiourea-based catalysts[6] to promote photoreactions with excellent control of product enantioselectivity.[5b] As an example, we showed that 4-alkenylcoumarin **1a** underwent a stereoselective [2+2] photocycloaddition to form photoproduct **2a** with 94% enantioselectivity with binaphthyl based thiourea catalysts.[5b] Having deciphered the importance of binaphthyl based thiourea catalysts we were interested in evaluating other thiourea skeletons to promote photochemical transformations. We were interested in the role of thioureas not only to achieve high enantioselectivity but also high conversions, as it will increase the type of skeletons that could be employed for controlling photoreactions. In this report we present our findings with six diverse thiourea catalysts **3b–g** in promoting the [2+2] photocycloaddition of coumarins **1a** and **1b**. (Scheme 1). The efficiencies of the new thiourea skeletons were compared to reaction efficiency with our previously established catalyst **3a** (prepared in one step from commercially available starting material) that gave quantitative conversions upon [2+2] photocycloaddition of **1a** leading to 74% enantiomeric excess (*ee*) in the photoproduct **2a**.

As we had previously established the optimal reaction conditions for the enantioselective [2+2] photocycloaddition of **1a** with catalyst **3a**, *viz.* 1:1 mixture of toluene and *meta*-xylene at −78±2 °C, we employed the same set of reaction conditions to evaluate the new thiourea skeletons and compare both reaction efficiencies and enantioselectivity (Table 1). Six thiourea skeletons,[7] were examined as they have been shown to be effective in promoting enantioselective



Scheme 1. Enantioselective [2+2] photocycloaddition of coumarin derivatives **1** mediated by thioureas **3**.

thermal transformations. These included the atropisomeric binaphthyl based bis-aryl thiourea **3b**,[7a] the C_2-symmetrical bis-thioureas **3c**[7b] and **3d**,[7c] and monofunctional chiral thiourea **3e**,[7d] Ricci's catalyst **3f**[7e,f] and **3g**.[7g]

To evaluate the efficiency of thiourea catalysts in promoting the [2+2] photocycloaddition of coumarins **1a** and **1b**, we initially scanned different catalysts at a loading level of 100 mol%. Upon examination of Table 1, it is quite clear that thioureas display interesting features while promoting photochemical reactivity and selectivity. We had previously established that thiourea **3a** was effective in promoting the photoreaction with an excellent *ee* value of 74%.[5b] Thiourea **3a** was also equally effective for **1b** leading to an *ee* value of 86% (Table 1; entry 2) with quantitative conversions. As we had previously established that **3a** forms both static and dynamic complexes with **1a** substrate promoting the photoreaction, we believe that a similar scenario manifests in the case of **1b** leading to high enantioselectivity in the corresponding photoproduct. As we had established the role of the naphthalene motif in promoting the intramolecular [2+2] photocycloaddition of coumarin **1a**, we evaluated another naphthyl based thiourea **3b**, in which we observed low *ee* values in the photoproduct. The reaction efficiency with **3b** was 89% and 100% for substrates **1a** and **1b**, respectively (Table 1; entry 3). To our surprise, C_2-symmetrical bis-thioureas **3c** and **3d**, as well as aminoindanol derived thiourea **3f** gave excellent conversions (Table 1; entries 4, 5 and 7), while monofunctional chiral thioureas **3e** and **3g** gave moderate conversions (Table 1; entries 6 and 8) albeit with low stereocontrol. This showed that thiourea can be effective in promoting the photochemical transformation. Analysis of Table 1 from a photochemical standpoint makes thioureas **3c** and **3f** stand out as they do not feature a light absorbing chromophore (compared to the coumarin functionality), yet were effective in promoting the photochemical reaction with excellent conversions. To further evaluate this observation, we carried out the photochemical transformation of **1a** and **1b** with sub-stoichiometric amounts of **3f** (10 mol%) and compared their reactivity with sub-stoichiometric amounts of **3a** and **3b** (Table 2).

Inspection of Table 2 reveals that even at 10 mol% loading, catalyst **3f** was effective in promoting the transformation. For example, the ratio of **1b**:**2b** was 0:100 (complete conversion) with catalyst **3a** under nitrogen atmosphere compared to 36:64 and 38:62 with

Table 1. Enantioselective intramolecular [2+2] photocycloaddition of **1a** with thioureas **3b**–**3g**.[a]

		1a			**1b**		
Entry	Catalyst	**1a**:**2a**[c]	% Conversion (**2a**)[d]	% *ee* (**2a**)[e]	**1b**:**2b**[c]	% Convversion (**2b**)[d]	% *ee* (**2b**)[e]
1	none	89:11	9	racemic	77:23	18	racemic
2	**3a**[b]	11:89	84	74	0:100	100	86
3	**3b**	6:94	89	28	0:100	100	14
4	**3c**	23:77	72	24 (*ent*-**2a**)	0:100[f]	100	24 (*ent*-**2b**)
5	**3d**	11:89	84	24	–	–	–
6	**3e**	52:48	45	4	–	–	–
7	**3f**	10:90[g]	91	racemic	0:100	100	22
8	**3g**	33:67[g]	57	racemic	–	–	–

[a] Reactions were carried out in 1:1 toluene/*meta*-xylene solvent mixture at −78 ± 2 °C for 3 h with 1 equivalent of the catalyst. All samples were degassed with N_2 bubbling for 8–10 min prior to irradiation. Values are an average of two trials.

[b] Values from ref.[5b]

[c] Ratios were obtained from GC analysis.

[d] Reaction conversions (%) were determined by ^{1}H NMR spectroscopy using triphenylmethane as internal standard. The mass balance was greater than 90% in all the trials.

[e] From GC analysis using chiral stationary phase.

[f] From ^{1}H NMR spectroscopy. GC analysis showed a ratio 3:97 for **1b**:**2b**.

[g] From ^{1}H NMR spectroscopy.

Table 2. Intramolecular [2+2] photocycloaddition of **1** with 10 mol% of catalyst **3** in 1:1 toluene/xylene.[a]

Entry	Catalyst	Compound	Conditions	**1**:**2**[b]	(% *ee*, **2**)[b]
1	none	**1b**	N_2/4 h	66:34	racemic
2	**3a**	**1b**	N_2/2 h	0:100	86
3	**3b**	**1b**	N_2/4 h	36:64	28
4	**3f**	**1b**	N_2/4 h	38:62	10
5			O_2/4 h	(56)[c]	12
6			air/4 h	55:45 37:63	12
7	**3f**	**1a**	N_2/4 h	68:32	0
8			O_2/4 h	78:22	0
9			air/4 h	71:29	0

[a] Solutions were sparged with the appropriate gas for 8–10 min prior to irradiation. Reactions at −78 ± 2 °C.

[b] Values were determined by GC analysis.

[c] Isolated yield, 6 h irradiation.

catalysts **3b** and **3f**, respectively (Table 2; compare entries 2–4). In addition, with catalyst **3f** the ratio of **1b**:**2b** was unaffected under nitrogen, oxygen and air saturated reaction atmospheres (Table 2; entries 4–6). Similarly, with catalyst **3f** the ratio of **1a**:**2a** was unaffected under nitrogen, oxygen and air saturated reaction atmospheres (Table 2; entries 7–9). This raises interesting questions: (a) How does catalyst **3f** promote the photochemical reaction? and (b) what is the mode of reactivity with the coumarin substrate? To address this we utilized coumarin substrate **1b** as a model system to understand the influence of thiourea **3f** in promoting the photochemical reaction.

To understand the nature of the interaction between the coumarin substrate and the thiourea, we carried out NMR titration experiments (Figure 1) and photophysical studies (Figure 2). Inspection of Figure 1 shows that thiourea interacted with the coumarin substrate, which was indicated by the upfield shift of the C-3 alkene proton resonance of **1b** upon addition of various equivalents of **3f**. The strength of the interaction was computed by non-linear regression analysis of the NMR titration experiments that revealed a binding constant[8] of 14.8 (±1.2) M^{-1} in $CDCl_3$ (Figure 1). UV-Vis spectra of catalyst **3f** and substrate **1b** (Figure 2, A) clearly showed that the coumarin substrate is absorbing the light at the irradiating wavelength (~350 nm) even at 100 mol% catalyst loading. Very weak fluorescence centred around 390 nm was observed from **1b** at room temperature in toluene (Figure 2, B). The excitation matched with the absorption spectra indicating that the emitting chromophore has its origin in the coumarin functionality (Figure 2, B). Time correlated single photon counting measurements on **1b** in toluene at room temperature showed that the fluorescence lifetime decay traces overlapped within the instrument response function indicating very short singlet lifetimes (< 0.1 ns). The short fluorescence lifetime is probably caused by fast intersystem crossing into the triplet state or fast [2+2] cycloaddition at room temperature. To decipher this, we recorded the luminescence in a solid matrix at 77 K, where [2+2] cycloaddition will be hindered. Figure 2, C (—) shows the steady-state luminescence spectrum of **1b** in toluene glass at 77 K with two major peaks at ~390 nm and ~500 nm that were assigned to fluorescence and phosphorescence, respectively. This peak assignment is consistent with the time-resolved luminescence spectrum recorded 10 ms after the excitation light pulse where only the long-lived phosphorescence is detectable (Figure 2, C

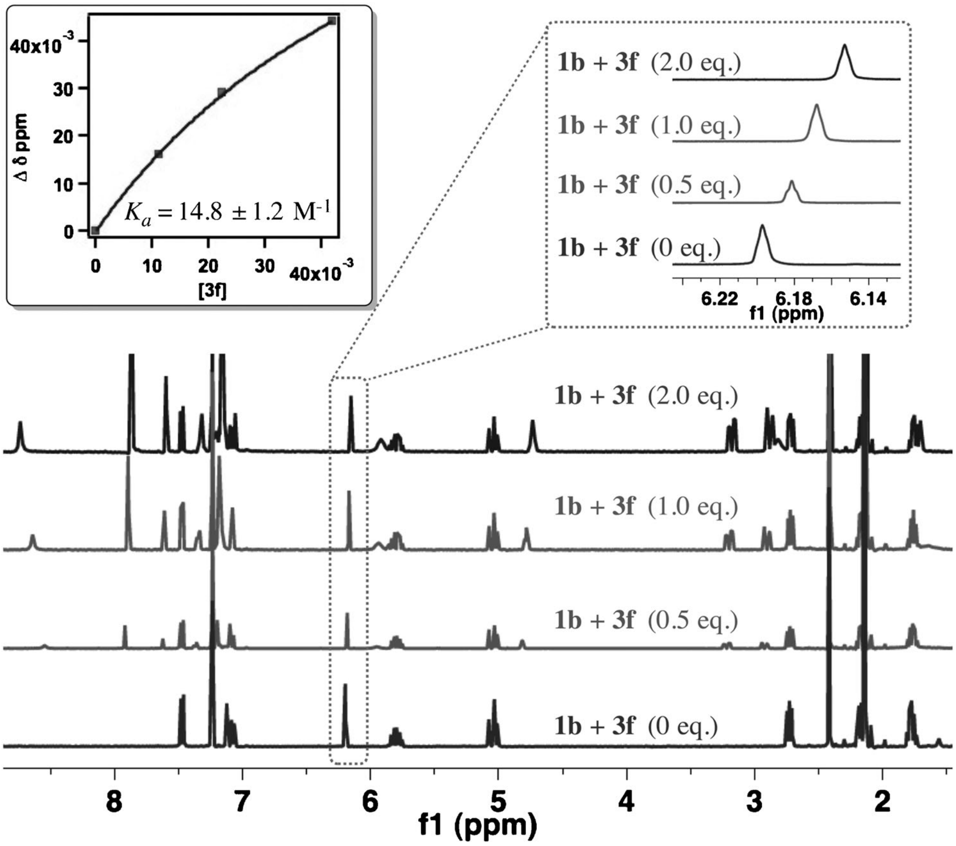


Figure 1. ^{1}H NMR spectra (400 MHz; $CDCl_3$) of **1b** [0.02 M] in the absence and in the presence [0.01–0.04 M] of catalyst **3f**. The expanded inset shows the upfield shift of the C-3 alkene proton in **1b** upon addition of various equivalents of the thiourea **3f**.

●●●). Time correlated single photon counting measurements on **1b** in toluene glass at 77 K showed that the fluorescence lifetime decay traces once again overlapped within the instrument response function indicating very short singlet lifetimes (< 0.1 ns) even at 77 K. Phosphorescence lifetime measurements at 77 K showed a biexponential decay with two distinct lifetimes 0.9 s and 0.3 s (the biexponential decay likely due to matrix inhomogeneity at 77 K) indicating a ππ* excited state (Figure 2, D).[9] These observations point to a fast decay of the singlet excited state due to intersystem crossing and/or internal conversion. Therefore, we conclude that, in the case of **1b**, photochemical reactivity likely occurs from the triplet excited state.

Based on the above observations, the role of **3f** in promoting the photoreaction of coumarin **1b** can be elucidated. We believe that **3f** interacts with **1a** in the ground state as evidenced by NMR titration experiments. Photoexcitation of **1b** in the presence of **3f** (stoichiometric or sub-stoichiometric) results in an extremely short-lived singlet excited state due to a very fast intersystem crossing rate and/or internal conversion resulting in the triplet-excited species. The lack of oxygen quenching points to a highly reactive triplet-excited state resulting in a 1,4-biradial that cyclizes to form the intramolecular [2+2] photocycloaddition product. A similar scenario manifests in the case of coumarin substrate **1a**.

Our study has revealed that thioureas can interact with coumarin substrates and promote photoreaction(s) with different modes of activation. The mode of activation depends on the type of chromophore and/or functionality attached to the thiourea motif that anchors the reactive substrate through hydrogen bonding. Manipulating the delicate balance as well as influencing non-bonding interactions that occur between the thiourea and reactive substrate can open up opportunities to develop organo-photocatalysts to enhance both reactivity and selectivity.[6]

Experimental Section

General Procedure for Photoreactions

Coumarin **1** (0.02 M) and thiourea **3a–g** (0.002–0.02 M) were dissolved in an appropriate solvent in a Pyrex test tube. The reaction mixture was degassed by nitrogen (oxygen or air) bubbling for 8–10 min. Then the resultant solution was irra-

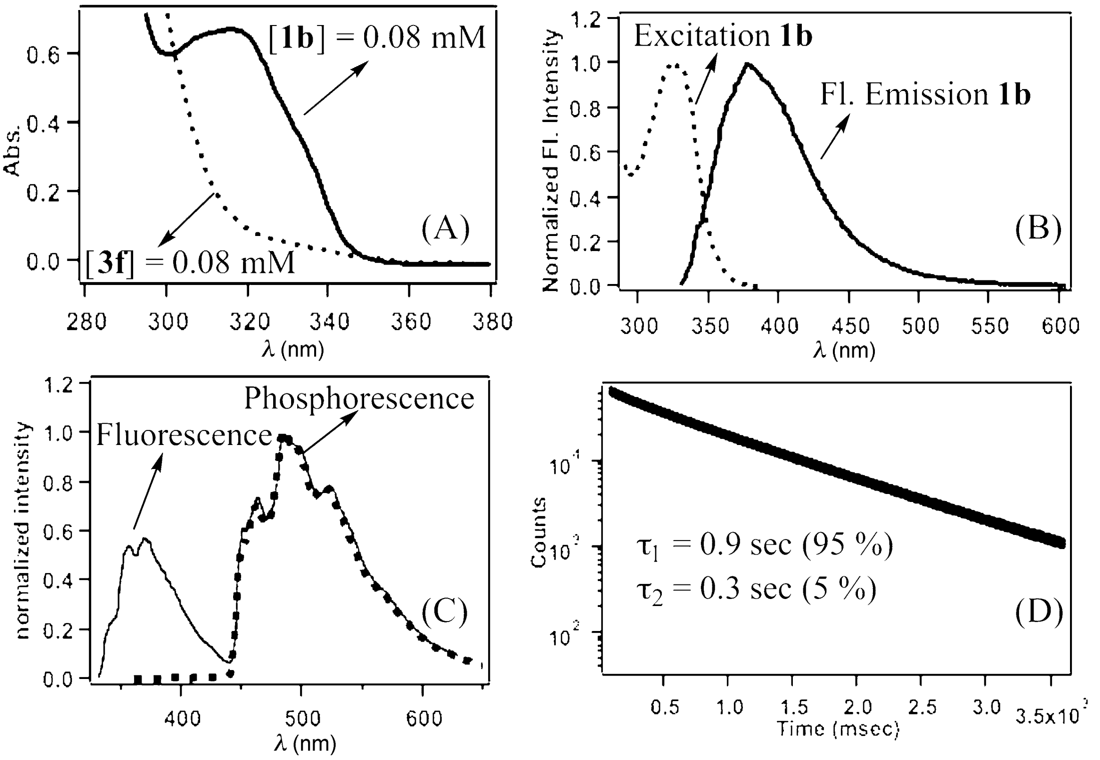


Figure 2. (A) UV-Vis spectra of **1b** (–) and **3 f** (●●●) in toluene. (B) Fluorescence emission (—) and excitation (●●●) of **1b** in toluene at room temperature. (C) Time-resolved phosphorescence spectrum (●●●) and steady state luminescence spectrum (—) of **1b** in toluene glass at 77 K. (D) Phosphorescence lifetime of **1b** in toluene glass at 77 K.

diated in Rayonet reactor (~350 nm) at −78±2 °C for the specified time intervals. The irradiated samples were analyzed by gas chromatography to ascertain the reactant to product ratio as well as the enantiomeric excess in the photoproduct. For conversion and mass balance studies, after irradiation for specific time intervals, an appropriate amount of internal standard (triphenylmethane) was added to the reaction mixture. The solvent was evaporated under reduced pressure in a rotary evaporator and was dried under high vacuum. The crude reaction mixture was analyzed by ^{1}H NMR spectroscopy ($CDCl_3$ as solvent).

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