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Photoswitchable Thioureas for the External Manipulation of Catalytic Activity

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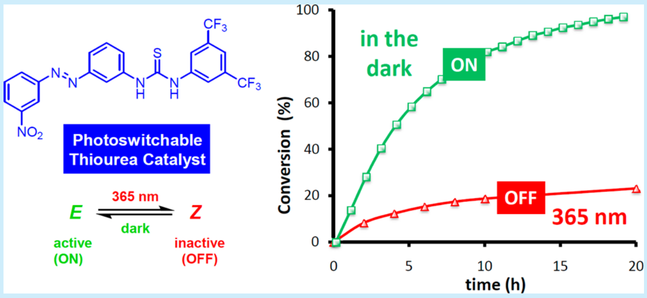
Supporting Information

ABSTRACT: A series of azobenzene-based thiourea catalysts have been developed with the aim of achieving control over the catalytic activity by the use of light. The conceptual design of these systems relies on the inactivation by means of intramolecular hydrogen bonding, only likely to take place in one of their isomeric forms. After fine structure modulation of the catalyst a substantial difference in activity has been observed between the irradiated and the nonirradiated reaction. Furthermore, the system allowed in situ manipulation of the catalyst activity during the course of a given experiment.



The field of catalysis has become one of the most important research topics in chemistry in recent decades, as it plays a crucial role in the efficient production of bulk and fine chemicals.[1] Traditionally, catalysts have been accurately designed for optimal execution in a given target reaction. However, in recent years there has been increasing interest in the development of smart catalytic systems, the function of which can be controlled at will. This can be realized by the use of multistate catalysts[2,3] and opens the door to a wide range of potential applications such as controlled drug delivery,[4] mimics of regulatory biocatalysts,[5] or for streamlined multistep syntheses. Different external stimuli have been exploited to induce the change in the state of the catalyst, including acid−base chemistry,[6] mechanical forces,[7] redox processes,[8] and light.[9] Among these, the use of light to trigger a response is especially appealing, as it constitutes a noninvasive stimulus that allows for exceptional spatial and temporal control. This can be easily attained by fine-tuning the intensity and the wavelength with an appropriate light source. Photoswitchable catalysts are generally based on photochromic moieties that are precisely incorporated within the molecular backbone. Several approaches have been addressed to obtain a substantial difference in catalytic activity between both states. When using spiropyrans or dithienylethenes as photoswitches, this difference is usually caused by a change in electronic properties.[10]

On the other hand, if the molecular switch is an *E*/*Z* photoisomerizable species (e.g., azobenzene) the activity can be modulated by changing the sterics around the catalytic center (Figure 1a; steric shielding)[11] or by modifying the relative disposition of two distal units so that they can act in a cooperative fashion (Figure 1b; cooperativity).[12] Additionally, this kind of photochromic compounds have been recently applied to photocontrol the aggregation/dissociation state of the catalyst.[13]

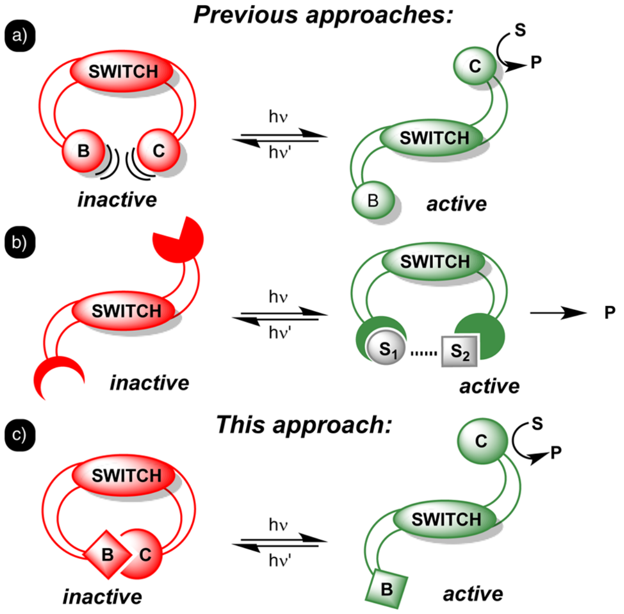


Figure 1. Different conceptual approaches of azobenzene-based photoswitchable catalysts. (a) Steric shielding; (b) cooperative activation; (c) inactivation by attractive intramolecular interactions (C: catalytic center; B: blocking agent; S: substrates; P: products).

In the present work we address the photomodulation of a catalyst from a different point of view. In particular, we envisioned a design featuring an attractive interaction between

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the active site and the blocking moiety, which could act as a driving force to generate the inactive state. This would greatly simplify the synthesis since rigid, bulky systems (mandatory for steric shielding-based photoswitches, Figure 1a) would no longer be necessary due to the reduction of the number of available conformers (Figure 1c).

We speculated that intramolecular H-bonding between appropriately placed donor and acceptor moieties could afford a suitable interaction, strong enough to block the active site when in the proper geometry but still allowing isomerization to take place. With this in mind, the initial design aimed to achieve a "blocked" catalyst in the ground *E*-state by placing a thiourea and a Lewis base moiety in opposite *ortho* positions of an azobenzene photoresponsive core. Hence, activation of the catalyst would be triggered by isomerization upon irradiation (Figure 2, top).

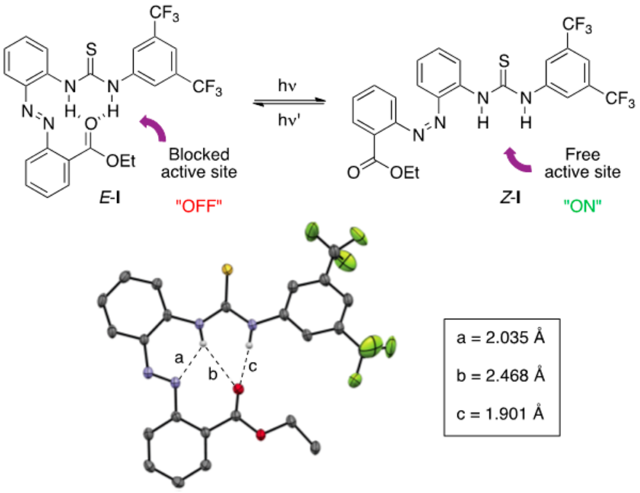


Figure 2. Initial design of the photoswitchable thiourea catalyst and X-ray of **I**.

Thus, compound **I** was easily prepared in four steps,[14] and its structure was confirmed by single crystal X-ray diffraction (Figure 2, bottom).[15] To our delight, the spatial arrangement in the solid phase evidenced intramolecular hydrogen bonding interactions between the N–H's of the thiourea and the oxygen atom of the carbonyl group, as initially envisaged. Indeed, when this compound was tested in the Michael addition of acetylacetone to *m*-bromonitrostyrene—the benchmark reaction used throughout this work[16]—it showed no additional reactivity with respect to the background reaction. This was a clear indication that the active site of **I** was completely blocked in its more stable *E* form. However, all attempts to induce the photoisomerization of this compound proved unsuccessful, and consequently no relevant activation was observed when performing the same reaction upon irradiation.[14]

A closer analysis of the X-ray revealed that this was an exceptionally stable structure. On one hand, one of the H-bonds between the ester and the thiourea proved to be particularly strong, with a N–H···O distance of <2 Å and a torsion angle of 173°.[17] On the other hand, as depicted in Figure 2, an additional H-bond was taking place between the N–H of the thiourea and one of the N-atoms of the azo group, an interaction that has been previously reported to prevent photoisomerization.[18]

With this in mind, we set our sights on the preparation of azothiourea catalysts in which the latter H-bonding interaction could not occur. Hence, we decided to revert the conceptual approach so that the new catalysts would be active in its *E* form and would become blocked after isomerization (Figure 3).

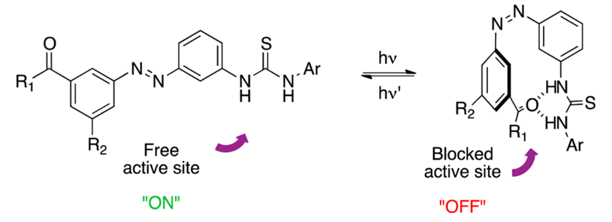


Figure 3. Schematic representation of the second design in which the catalyst would become blocked after *Z*-isomerization.

In this second approach the two functionalities (the thiourea H-bond donor and the Lewis base "blocking moiety") were both located in the *meta* position of opposite phenyl rings of the azobenzene. Taking this into consideration, four different potential catalysts were designed aiming to evaluate the effect of the Lewis base scaffold. Thus, amides **II**–**III**, ester **IV**, and nitro **V** (Figure 4) were synthesized,[14] following a procedure analogous to that for compound **I**. Noteworthy, the structure of the amide derivative **II** could be confirmed by X-ray diffraction,[19] which shows that no intramolecular H-bonding interactions are likely to arise in this structure.[14]

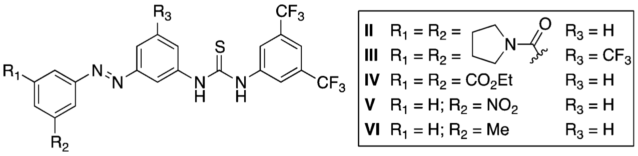
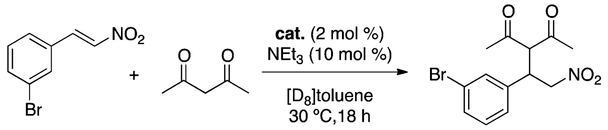


Figure 4. Set of catalysts prepared following the second design.

As shown in Table 1, among the catalysts selected, the nitro derivative **V** displayed the highest activity, giving almost full conversion after 18 h. It should also be noted that there is a slight background reaction in the absence of catalyst.

Table 1. Catalytic Activity of Azocompounds II–V in the Dark



catalyst	conv[a] (%)
none	11
II	38
III	58
IV	86
V	96

[a]Conversion was measured *in situ* by ^{1}H NMR after 18 h.

Once the catalytic activity of these azobenzene-based thiourea catalysts was satisfactorily verified, we proceeded to study their photochromic behavior by UV/vis spectroscopy[14] and quantify their photostationary states (PSS) by ^{1}H NMR. In this regard, it is important to mention that since the PSS can be strongly influenced by several parameters such as concentration, solvent, or temperature,[20] the irradiation experiments were performed under the specific conditions of the reaction of choice. Among the four catalysts prepared, the nitro derivative **V** showed the best PSS (56% *Z* after 2.5 h of irradiation at 365 nm; Table 2, entry 4). Noteworthy, better PSSs were observed under more diluted conditions (70% *Z* at 1.5 mM for catalyst **V**), albeit this concentration was not useful for catalytic purposes.

Table 2. Photochromic Properties of Thiourea Catalysts II–V[a]

			PSS[b]		
entry	catalyst	irradiation time (h)	E→Z (Z/E)	Z→E (E/Z)	$\tau_{1/2}$ (h)[b,c]
1	**II**	5	34/66	98/2	8
2	**III**	2	15/85	>99/1	2
3	**IV**	0.5	48/52	90/10	48
4	**V**	2.5	56/44	99/1	3

[a] Reaction conditions: the experiments were performed in a quartz NMR tube without stirring, with irradiation at 365 nm and 2.5 mM of catalyst in [D$_8$]toluene at *t* = 30 °C. [b] Measured by ^{1}H NMR. [c] *t* = 20 °C.

Considering that the nitro derivative **V** showed both the best catalytic profile and the most convenient PSS,[21] it was selected to continue with further investigation. Figure 5a illustrates the progress of the reaction between acetylacetone and *m*-bromonitrostyrene mediated by **V** in the dark, in which the formation of 3-(1-(3-bromophenyl)-2-nitroethyl)pentane-2,4-dione was plotted versus time (green curve). Under these conditions, full conversion was observed after 19 h (v_0 = 0.0176 M·h^{-1}). Remarkably, when the same experiment was performed under irradiation at 365 nm the reaction turned out to be substantially slower, reaching only 23% conversion after 20 h (v_0 = 0.0051 M·h^{-1}, Figure 5a, red curve). Furthermore, the catalyst could be switched "ON"–"OFF" within the course of the reaction by application of UV light after 4 h in the dark (Figure 5b, purple curve). Finally, the "OFF" state of the catalyst could be further reactivated simply by stopping irradiation and keeping the reaction in the dark (Figure 5c, blue curve). Although the change was not dramatic, likely due to the fact that the thermal back isomerization is not instantaneous, an increase in reaction rate could be clearly perceived in comparison with the same reaction performed upon continuous irradiation.

Finally, in order to evaluate whether the factor responsible for the inactivation of the catalyst was indeed an H-bonding interaction, rather than a mere steric effect, an analogous catalyst was prepared in which the nitro group was replaced by a methyl substituent (**VI**, Figure 4). As depicted in Figure 5d, this catalyst proved less active than **V** in the dark (64% vs 96% conv after 18 h). Under UV irradiation, the conversion decreased to 43% in 18 h (vs *ca.* 21% with **V**), which seems to indicate that the active site in the *Z* form is, in any case, less accessible. However, the difference in activity between the ON and OFF states of the nitro counterpart **V** is substantially more pronounced than that of **VI**, which supports a significant contribution of H-bonding to the blocking of the active site.

In conclusion, a photoswitchable thiourea organocatalyst has been synthesized, which very efficiently catalyzed the Michael addition of acetylacetone to *m*-bromonitrostyrene in its thermodynamically more stable *E* form. In turn, when the same reaction was performed upon UV irradiation, which led to the isomerization of the catalyst, the reaction rate turned out to be significantly lower, thus demonstrating the blocking of the active site. Furthermore, the state of the catalyst could be in situ manipulated both to activate or inactivate the catalyst during the course of a given reaction.

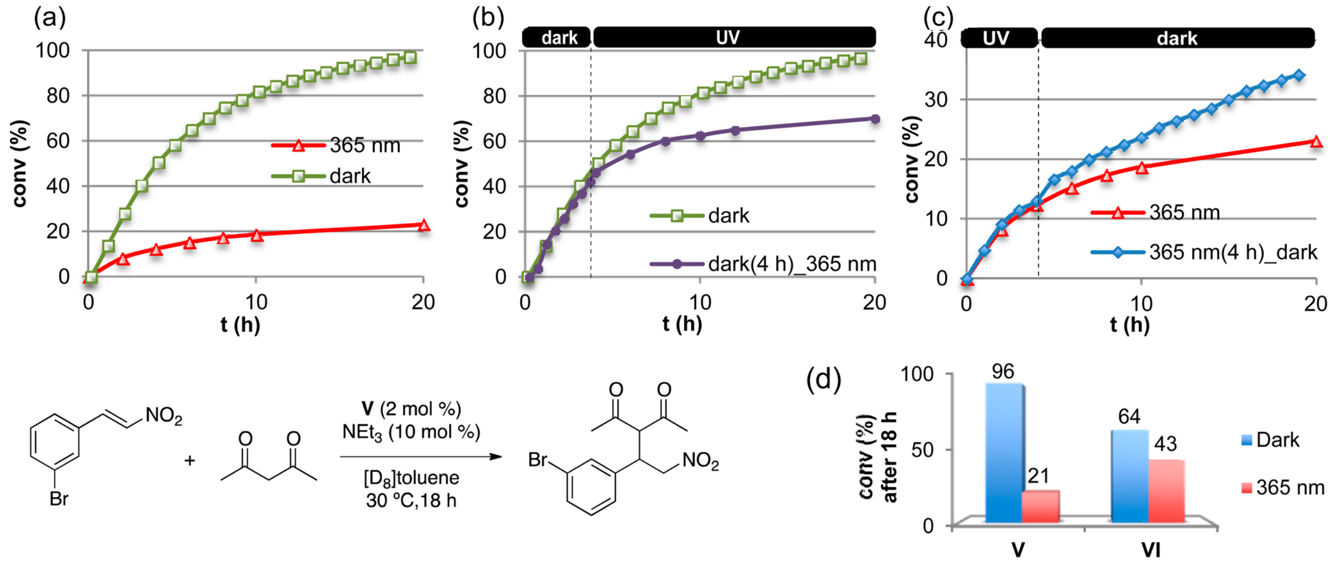


Figure 5. (a) Michael addition catalyzed by **V** in the dark (green) and upon UV irradiation (red). (b) With "ON"–"OFF" switching of the state of catalyst **V**, the reaction starts rapidly in the dark and slows down upon UV exposure (purple). (c) With "OFF"–"ON" switching of the state of catalyst **V**, the reaction proceeds slowly while being irradiated and accelerates in the dark (blue). (d) Comparison between the activity of **V** and **VI** in the ON and OFF states.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, UV/vis studies, and 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 interest.

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■ REFERENCES

(1) (a) Roberts, S. M.; Poignant, G.; Kozhevnikov, I.; Xiao, J.; Whittall, J.; Pickett, T. E.; Derouane, E. G., Eds.; *Catalysis for Fine Chemical Synthesis*, Vol. *1*−*5*; John Wiley & Sons: NJ, 2004. (b) van Leeuwen, P. W. M. N. *Homogeneous Catalysis: Understanding the Art*; Kluwer: Dordrecht, 2004.

(2) Recent reviews on artificial switchable catalysis: (a) Kovbasyuk, L.; Krämer, R. *Chem. Rev.* **2004**, *104*, 3161−3188. (b) Stoll, R. S.; Hecht, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5054−5075. (c) Dai, Z.; Lee, J.; Zhang, W. *Molecules* **2012**, *17*, 1247−1277. (d) Sohtome, Y.; Nagasawa, K. *Chem. Commun.* **2012**, *48*, 7777−7789. (e) Kumagai, N.; Shibasaki, M. *Catal. Sci. Technol.* **2013**, *3*, 41−57.

(3) Recent reviews on supramolecular allosteric catalysis: (a) Zhu, L.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1190−1196. (b) Scrimin, P.; Prins, L. J. *Chem. Soc. Rev.* **2011**, *40*, 4488−4505.

(4) Shrestha, N. K.; Macak, J. M.; Schmidt-Stein, F.; Hahn, R.; Mierke, C. T.; Fabry, B.; Schmuki, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 969−972.

(5) (a) Keiper, S.; Vyle, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3306−3309. (b) Wang, G.; Kuroda, K.; Enoki, T.; Grosberg, A.; Masamune, S.; Oya, T.; Takeoka, Y.; Tanaka, T. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9861−9864. (c) Fruk, L.; Rajendran, V.; Spengler, M.; Niemeyer, C. M. *ChemBioChem* **2007**, *8*, 2195−2198.

(6) (a) Blanco, V.; Carlone, A.; Hänni, K. D.; Leigh, D. A.; Lewandowski, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5166−5169. (b) Yoon, H. J.; Junpei, K.; Kim, J.-H.; Mirkin, C. A. *Science* **2010**, *330*, 66−69. (c) Schmittel, M.; De, S.; Pramanik, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3822−3826. (d) Balof, S. L.; P'Pool, S. J.; Berger, N. J.; Valente, E. J.; Shiller, A. M.; Schanz, H.-J. *Dalton Trans.* **2008**, *42*, 5791−5799. (e) Balof, S. L.; Yu, B.; Lowe, A. B.; Ling, Y.; Zhang, Y.; Schanz, H.-J. *Eur. J. Inorg. Chem.* **2009**, *13*, 1717−1722.

(7) (a) Wiggins, K. W.; Hudnall, T. W.; Tennyson, A. G.; Bielawski, C. W. *J. Mater. Chem.* **2011**, *21*, 8355−8359. (b) Tennyson, A. G.; Wiggins, K. M.; Bielawski, C. W. *J. Am. Chem. Soc.* **2010**, *132*, 16631−16636. (c) Karthikeyan, S.; Potisek, S. L.; Piermattei, A.; Sijbesma, R. P. *J. Am. Chem. Soc.* **2008**, *130*, 14968−14969.

(8) (a) Allgeier, A. M.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 894−908. (b) Lorkovic, I. M.; Duff, R. R.; Wrighton, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 3617−3618. (c) Gregson, C. K. A.; Gibson, V. C.; Long, N. J.; Marshall, E. L.; Oxford, P. J.; White, A. J. P. *J. Am. Chem. Soc.* **2006**, *128*, 7410−7411. (d) Broderick, E. M.; Guo, N.; Vogel, C. S.; Xu, C.; Sutter, J. R.; Miller, J. T.; Meyer, K.; Mehrkhodavandi, P.; Diaconescu, P. L. *J. Am. Chem. Soc.* **2011**, *133*, 9278−9281. (e) Broderick, E. M.; Guo, N.; Wu, T.; Vogel, C. S.; Xu, C.; Sutter, J.; Miller, J. T.; Meyer, K.; Cantat, T.; Diaconescu, P. L. *Chem. Commun.* **2011**, *47*, 9897−9899.

(9) For recent reviews, see: (a) Neilson, B. M.; Bielawski, C. W. *ACS Catal.* **2013**, *3*, 1874−1885. (b) Göstl, R.; Senf, A.; Hecht, S. *Chem. Soc. Rev.* **2014**, *43*, 1982−1996.

(10) (a) Niazov, T.; Shlyahovsky, B.; Willner, I. *J. Am. Chem. Soc.* **2007**, *129*, 6374−6375. (b) Wilson, D.; Branda, N. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 5431−5434. (c) Neilson, B. M.; Bielawski, C. W. *J. Am. Chem. Soc.* **2012**, *134*, 12693−12699. (d) Neilson, B. M.; Bielawski, C. W. *Chem. Commun.* **2013**, *49*, 5453−5455. (e) Neilson, B. M.; Bielawski, C. W. *Organometallics* **2013**, *32*, 3121−3128.

(11) (a) Ueno, A.; Takahashi, K.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1981**, *3*, 94−96. (b) Sugimoto, H.; Kimura, T.; Inoue, S. *J. Am. Chem. Soc.* **1999**, *121*, 2325−2326. (c) Peters, M. V.; Stoll, R. S.; Kühn, A.; Hecht, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5968−5972. (d) Stoll, R. S.; Peters, M. V.; Kühn, A.; Heiles, S.; Goddard, R.; Bühl, M.; Thiele, C. M.; Hecht, S. *J. Am. Chem. Soc.* **2009**, *131*, 357−367. (e) Stoll, R. S.; Hecht, S. *Org. Lett.* **2009**, *11*, 4790−4793.

(12) (a) Würthner, F.; Rebek, J., Jr. *J. Chem. Soc., Perkin Trans. 2* **1995**, *9*, 1727−1734. (b) Würthner, F.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1995**, *34*, 446−448. (c) Cacciapaglia, R.; Di Stefano, S.; Mandolini, L. *J. Am. Chem. Soc.* **2003**, *125*, 2224−2227. (d) Imahori, T.; Yamaguchi, R.; Kurihara, S. *Chem.—Eur. J.* **2012**, *18*, 10802−10807. (e) Wang, J.; Feringa, B. L. *Science* **2011**, *331*, 1429−1432.

(13) (a) Wei, Y.; Han, S.; Kim, J.; Soh, S.; Grzybowski, B. A. *J. Am. Chem. Soc.* **2010**, *132*, 11018−11020. (b) Nojiri, A.; Kumagai, N.; Shibasaki, M. *Chem. Commun.* **2013**, *49*, 4628−4630.

(14) See Supporting Information for details.

(15) Nonrelevant H atoms have been hidden for clarity. CCDC 976348 contains the crystallographic data for thiourea **I**. These can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119−125.

(17) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. *Pure Appl. Chem.* **2011**, *83*, 1637−1641.

(18) Bandara, H. M. D; Friss, T. R.; Enriquez, M. M.; Isley, W.; Incarvito, C.; Frank, H. A.; Gascon, J.; Burdette, S. C. *J. Org. Chem.* **2010**, *75*, 4817−4827.

(19) CCDC 976349 contains the crystallographic data for thiourea **II**. These can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(20) Gauglitz, G. In *Photochromism. Molecules and Systems*; Duerr, H., Bouas-Laurent, H., Eds.; Elsevier, Amsterdam, 1990; pp 15−63.

(21) The ester derivative **IV** performed similarly to **V**, but it was discarded due to poor fatigue resistance (photodecomposition products started to appear after 30 min of UV irradiation). The nitro derivative **V** turned out to be much more robust.