Organocatalysis **Hot Paper**

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Disulfide-Catalyzed Visible-Light-Mediated Oxidative Cleavage of C=C Bonds and Evidence of an Olefin–Disulfide Charge-Transfer Complex

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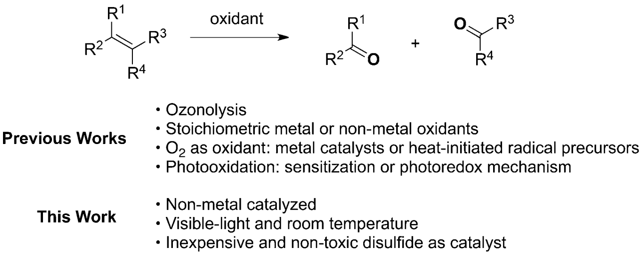
Abstract: *A photocatalytic method for the aerobic oxidative cleavage of C=C bonds has been developed. Electron-rich aromatic disulfides were employed as photocatalyst. Upon visible-light irradiation, typical mono- and multi-substituted aromatic olefins could be converted into ketones and aldehydes at ambient temperature. Experimental and computational studies suggest that a disulfide–olefin charge-transfer complex is possibly responsible for the unconventional dissociation of S–S bond under visible light.*

The oxidative cleavage of olefins (OCO) is a widely applied transformation in organic synthesis, since it introduces oxygen-containing functional groups such as ketones and aldehydes from inexpensive olefinic feedstock.[1] Despite the simplicity of the reaction, a practical and mild OCO method is still one of the long-sought goals in the development of modern chemical methods. One of the most popular methods for this transformation is still the old-fashioned ozonolysis,[2] which requires an ozone generator and displays serious safety issues owing to the toxicity of O_3. Modern OCO reactions include methods employing stoichiometric metal or non-metal reagents that are either toxic or strongly oxidizing,[1] or methods that utilizing molecular oxygen as a safer and cleaner oxidant in combination of catalytic amount of transition-metal complexes[3–5] or heat-initiated radical precursors (such as NHPI[6] or AIBN[7]). Recently, photochemical OCO methods have been reported with the photon as a traceless reagent and a green source of energy.[8–12] In general, these methods require UV light, or catalysts that are toxic[8] or metal-based,[9] or a demandingly oxidative photoredox catalyst to be SET-reduced by the olefin.[10–12] Alternatively, it would be attractive to seek a non-metal photocatalyst that functions via a non-redox/sensitization mechanism, and preferably with a reduced cost than most photocatalysts. Herein, we report a visible-light aerobic OCO method that utilizes inexpensive aromatic disulfide as photocatalyst (Scheme 1).



Previous Works
- Ozonolysis
- Stoichiometric metal or non-metal oxidants
- O_2 as oxidant: metal catalysts or heat-initiated radical precursors
- Photooxidation: sensitization or photoredox mechanism

This Work
- Non-metal catalyzed
- Visible-light and room temperature
- Inexpensive and non-toxic disulfide as catalyst

Scheme 1. Summary of previous OCO methods.

Several previously reported radical-catalyzed OCO reactions involved the formation of a dioxetane that decomposes to give the product aldehyde or ketone.[3,6,7] In seeking a photoinitiated radical that could reversibly add to the C=C bond, we envisioned that the thiyl radical generated by the photolysis of disulfide could serve as an ideal catalyst.[13,14] Recently, examples of disulfide-catalyzed photoreactions were reported, in which disulfide undergoes photolysis to catalyze the diboration of terminal alkynes,[15a] or the reduction of a carbon–halide bond with NHC-borane,[15b] or the [3+2] cycloaddition.[15c] They required light from the UV region because the dissociation of typical aromatic S–S bond cannot occur under visible light.[16]

In the hope of establishing a photocatalytic OCO method with visible light instead of the harmful and equipment-demanding UV light, we were intrigued by the acceleration effect in the thiol–olefin co-oxidation (TOCO) reported and studied in-depth decades ago.[17–21] In the presence of an olefin, the overall rate for the oxidation–addition sequence is significantly faster than the SET oxidation of thiol alone, owing to the formation of an olefin–thiol charge-transfer complex (CTC; Scheme 2).[17,18] To the best of our knowledge, the same effect between olefin and disulfide has not been reported to date. Recently, photochemical activity of electron donor–acceptor complex (EDA complex) formed in situ[22–24]

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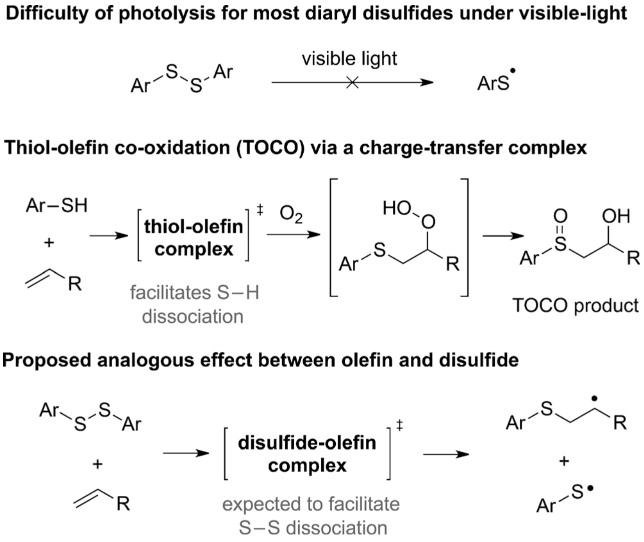
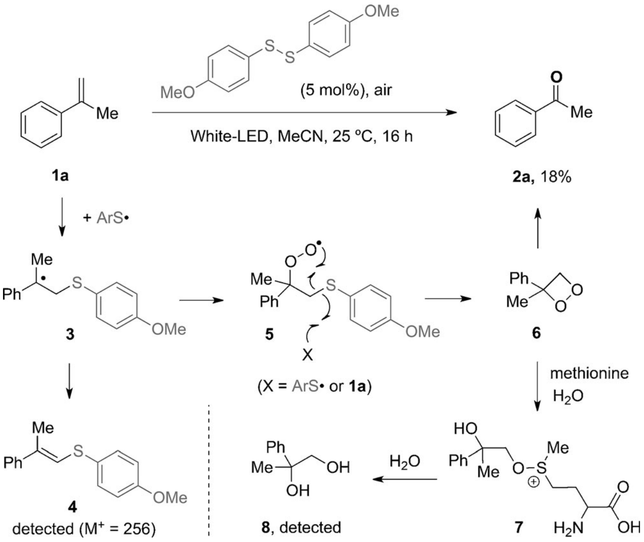


Scheme 2. Thiol–olefin co-oxidation (TOCO) and possible analogous effect between olefin and disulfide.

has been reported by Melchiorre,[25] in which two photo-inactive species transiently associate together to form a complex that is photoactive. Therefore, we envisioned that an analogous effect of TOCO/CTC might exist between disulfide and olefin, which could lead to a more feasible S–S bond photolysis by visible light in the presence of an olefin (Scheme 2).

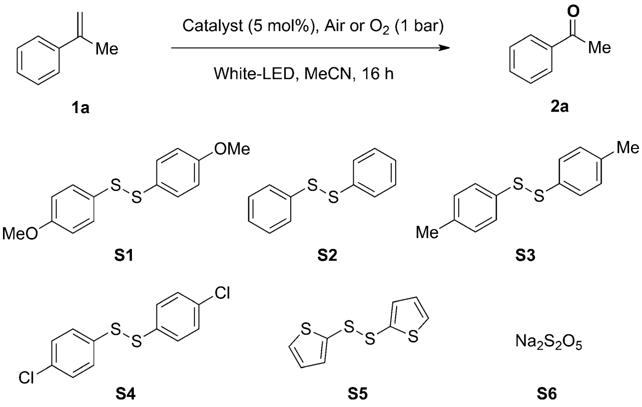
We initiated our study with a simple experiment in which the MeCN solution of α-methylstyrene (**1a**) and bis(4-methoxyphenyl) disulfide (**S1**, 5 mol%) was placed under light generated from a white LED lamp and stirred for 16 h with the reaction vial open to air. Gratifyingly, some of the C=C bond was found to be cleaved, and acetophenone (**2a**) was obtained in 18% isolated yield (Scheme 3). Like in other radical-mediated OCO methods, we also believed that the key intermediate was the dioxetane (**6**), which was formed from intermediate **5** by the abstraction[26] and substitution of the thiyl radical. Although dioxetane **6** could not be directly observed since it spontaneously decomposed upon formation[6,7] to give product **2a**, several observations were informative to confirm the proposed pathway: 1) The tertiary radical (**3**) from the thiyl addition underwent α-hydrogen abstraction to give trace amount of compound **4**, which was observed by GC-MS; 2) When the reaction was performed in the presence of methionine (1 equiv) and water as the trapping reagents for dioxetane,[27] the formation of diol **8** was detected.



Scheme 3. Visible-light oxidative C=C bond cleavage catalyzed by bis(4-methoxyphenyl) disulfide.

A set of experiments was performed to confirm the efficacy of disulfides as photo-precatalysts. In the absence of disulfide **S1**, no ketone product was observed (Table 1, entry 1). The dark reaction in the presence of **S1**, either at ambient temperature (entry 2) or heated to 45 °C (entry 3), afforded no observable product. The reaction in the presence of molecular oxygen (1 bar) gave an elevated yield of 83% (Table 1, entry 4) compared to the reaction under air. We also examined other disulfides such as bis(phenyl), bis(*p*-tolyl), bis(*p*-chlorophenyl),[28] and bis(2-thiophenyl) disulfides (**S2**–**S5**, entries 5–8), which all gave lower yields than **S1**. Inorganic compounds with an S–S bond, such as sodium metabisulfite (**S6**), were also examined; however, no ketone **2** was formed after 16 hours (entry 9).

Table 1: Exploring reaction conditions.



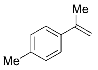
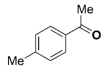
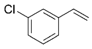
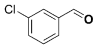
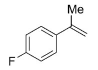
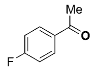
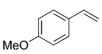
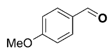
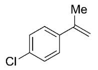
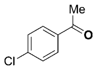
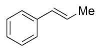
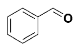
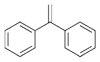
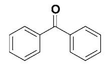
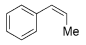
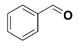
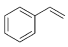
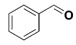
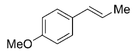
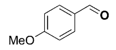
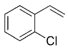
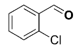
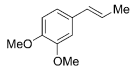
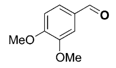
Entry	Catalyst	Oxidant	Light	T [°C]	Yield [%][a]
1	none	air	white LED	25	0
2	**S1**	air	dark	25	0
3	**S1**	air	dark	45	0
4	**S1**	O_2	white LED	25	83
5	**S2**	O_2	white LED	25	53
6	**S3**	O_2	white LED	25	72
7	**S4**	O_2	white LED	25	70
8	**S5**	O_2	white LED	25	29
9	**S6**	O_2	white LED	25	0

[a] Based on yields of isolated product.

With the optimal disulfide confirmed as **S1**, we set out to explore more olefinic substrates. At room temperature, a diverse set of aromatic olefins could be converted into corresponding ketones and aldehydes with 1 bar of O_2 and catalytic amount of **S1** (Table 2). The reaction with α-

Table 2: Disulfide-catalyzed photo-oxidation of aromatic olefins.

$$\text{Olefin} \xrightarrow[\text{white-LED, MeCN, 25 °C, 16 h}]{\textbf{S1}\text{ (5 mol\%), }O_2\text{ (1 bar)}} \text{Ketone / Aldehyde}$$

Olefin	Product and Yield[a]	Olefin	Product and Yield[a]
 **1b**	 **2b**, 91%	 **1h**	 **2h**, 75%
 **1c**	 **2c**, 92% c	 **1i**	 **2i**, 77%
 **1d**	 **2d**, 87%	 **1j**	 **2j**, 79% d
 **1e**	 **2e**, 76% b,c	 **1k**	 **2k**, 44% e
 **1f**	 **2f**, 73% c	 **1l**	 **2l**, 76%
 **1g**	 **2g**, 75%	 **1m**	 **2m**, 60%

[a] Based on yields of isolated product. [b] With 10 mol% catalyst. [c] Acetone as solvent. [d] 1,4-Dioxane as solvent. [e] Methanol as solvent.

methylstyrene analogues (**1b**–**1d**) all afforded excellent yields of the ketone products (**2b**-**2d**). Benzophenone (**2e**) could be prepared from 1,1-diphenylethylene (**1e**) in 76% yield, which however required more catalyst (10 mol%). Styrene and its derivatives with *ortho*-, *meta*-, and *para*-substituents (**1f**–**1i**) could all be converted into the aldehyde products in 70–80% yield. In general, the oxidation of 1,2-disubstituted olefins (**1j**–**1m**) also went smoothly and moderate to good yields were obtained, with the only exception of the reaction of (*Z*)-β-methylstyrene (**1k**), in which a part of the starting material either isomerized to the (*E*)-alkene (**1j**) or was epoxidized.

It is commonly believed that the photolysis of most aromatic disulfides requires UV irradiation.[13,15,16] To confirm that the light from the LED light source was not able to generate the thiyl radical from the disulfide, we carried out two control experiments. Under white LED light, the disulfide–disulfide exchange between bis(4-methoxyphenyl) disulfide (**S1**) and dimethyl disulfide (**S7**) did not take place (Scheme 4). In contrast, the mixture disulfide formed with 9% yield in 1 hour with irradiation from a medium-pressure Hg lamp. The reason a dialkyl disulfide was chosen for the cross-over experiment was that the exchange between two aromatic disulfides can occur via a concerted mechanism without light.[29–31] The photoaddition of disulfide to terminal alkyne under UV was first observed for dialkyl disulfide by Heiba and Dessau in 1960s.[32] A recent example was reported by Ogawa[14] in which diphenyl disulfide could be trapped by 1-octyne with light from a medium-pressure Hg lamp. However, under LED irradiation, an equimolar mixture of 1-heptyne and diphenyl disulfide (**S2**) did not undergo any addition reaction. These results suggested that the S–S bond of common aromatic disulfides cannot be cleaved to give thiyl radicals with light from an LED lamp (Scheme 4).

Thus, it is reasonable to assume that the olefin and disulfide have interactions that facilitate the S–S bond photolysis, with the olefin acting as a sensitizer. Following Szmant's procedure to confirm the thiol–olefin charge-transfer complex in the 1980s,[21a] we carried out a set of NMR experiments to seek evidence of the disulfide–olefin complex. By analyzing a series of ^{1}H NMR of a fixed amount of disulfide **S1** mixed with increasing amounts of α-methylstyrene (**1a**), we found that the chemical shift of the disulfide methoxy group distinctly drifted upfield, which indicated that the electron density on the disulfide had increased. This observation could be explained by the electron-donation from the olefin's conjugated π-system to the sulfur atom, based on the same observation and rationalization for the thiol–olefin system.[18–21] The chemical shifts for the olefin remained largely unchanged. The slope of the curve decreased with the increasing relative concentration of olefin, indicating that the charge-transfer complex was forming towards saturation (Figure 1).

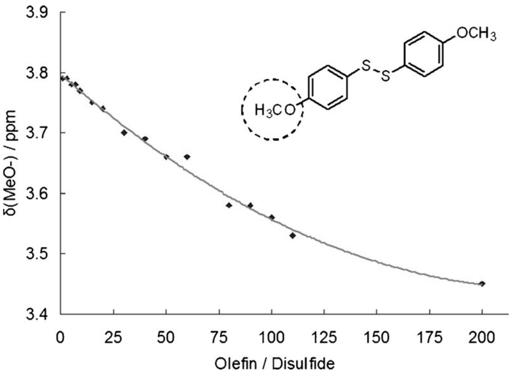
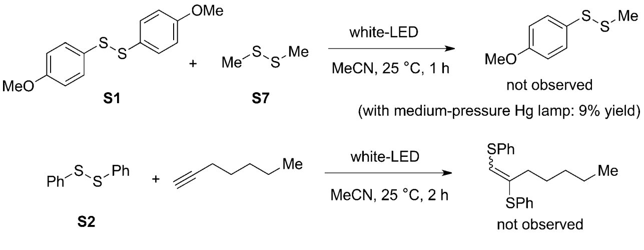


Figure 1. Correlation between the chemical shift of the OMe group of **S1** and the relative olefin concentration.



Scheme 4. The control experiments.

Along with experimental results, computational studies were also performed for the disulfide–olefin charge-transfer complex. The UV/Vis spectra[33,34] of **S1** and the complex **S1-1a** were simulated by DFT calculation at the ωB97x-D/6-31G* level of theory, which was previously used for theoretical studies of the spectroscopic behavior of various disulfides.[35] The energy and UV/Vis spectrum of **S1** were first calculated to confirm the accuracy of the method. The energy gap between HOMO (−7.83 eV) and LUMO (+0.59 eV) was calculated to be 8.42 eV (Figure 2). The calculated absorption of **S1** fell within the UV region (<400 nm, Figure 3) and was in accord with the experimental spectrum (see the Supporting Information).

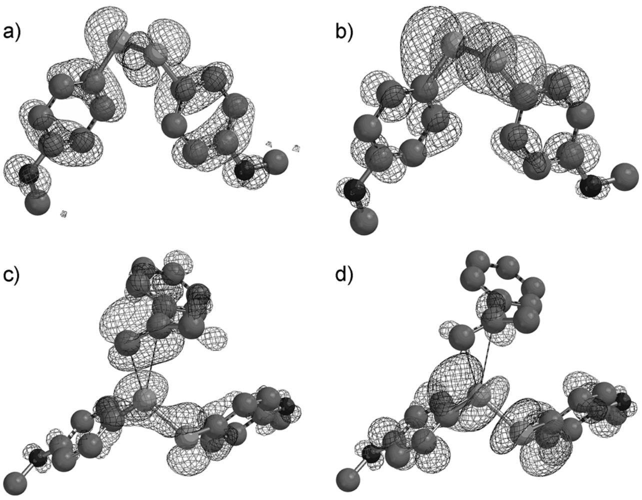


Figure 2. Modeling of the disulfide–olefin complex and energy levels by DFT calculation: a) HOMO (**S1**) $= -7.83$ eV, b) LUMO (**S1**) $= +0.59$ eV, c) HOMO (**S1-1a**) $= -6.89$ eV, d) LUMO (**S1-1a**) $= +0.42$ eV.

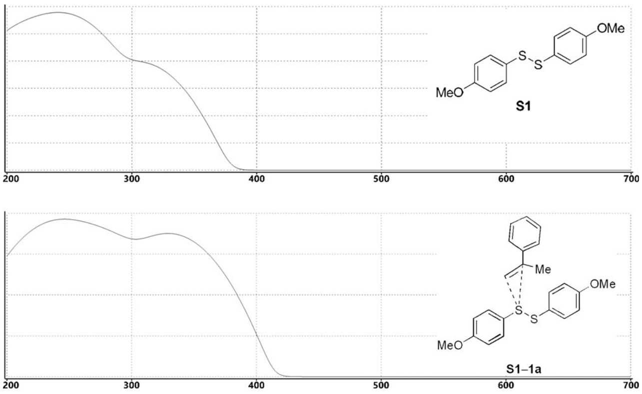


Figure 3. The simulated UV/Vis spectra of **S1** (top) and the disulfide–olefin complex **S1-1a** (bottom).

The structure of the disulfide–olefin complex (**S1-1a**) was proposed based on the results of NMR experiments that the electron density at the disulfide was increased, and also based on Fava[18] and Szmant's[20,21] models that the HOMO of the olefin preferably interacts with the LUMO of the thiol (here it is the LUMO of the disulfide). The geometry of the complex was optimized based on the same DFT method (ωB97x-D/6-31G*) for calculating the energy of **S1**. The disulfide–olefin complex (**S1-1a**) displayed a reduced HOMO–LUMO gap of 7.31 eV (HOMO -6.89 eV, LUMO $+0.42$ eV) as compared to that of the free disulfide **S1** (Figure 2). The reduced HOMO–LUMO gap might be attributed to the elevation of HOMO caused by the electron-donation from the C=C π-orbital to the sulfur (as shown in Figure 2).[21a] The calculated UV/Vis spectrum of the complex (**S1-1a**) showed that the range of absorption had extended to the visible region (400–430 nm) (Figure 3). Therefore, the olefin-activated disulfide would lead to a more feasible homolytic S−S bond dissociation under visible light, and a subsequent thiyl addition to the C=C bond.

In conclusion, we have developed a mild and non-metal-catalyzed method for the aerobic oxidative cleavage the C=C bond under visible-light at room temperature. Bis(4-methoxyphenyl) disulfide was employed as photocatalyst, and typical monosubstituted as well as 1,1- and 1,2-disubstituted aromatic alkenes could be converted into corresponding aldehydes and ketones. Interestingly, we have discovered that the coordinating effect between thiols and olefins might also exist between certain disulfides and olefins. The unconventional homolysis of the aromatic S−S bond by visible light was rationalized by the olefin–disulfide charge-transfer complex. Mechanistic details of this effect and more synthetic applications are currently being investigated in our lab.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: disulfide catalysts · donor–acceptor complexes · olefin oxidation · organocatalysis · visible-light photocatalysis

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[1] For Reviews on oxidative cleavage of olefins, see: a) A. Rajagopalan, M. Lara, W. Kroutil, *Adv. Synth. Catal.* **2013**, *355*, 3321–3335; b) J.-P. Wan, Y. Gao, L. Wei, *Chem. Asian J.* **2016**, *11*, 2092–2102.

[2] R. Criegee, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 745–752; *Angew. Chem.* **1975**, *87*, 765–771.

[3] A. Gonzalez-de-Castro, J.-L. Xiao, *J. Am. Chem. Soc.* **2015**, *137*, 8206–8218.

[4] a) A. Rubinstein, P. Jiménez-Lozanao, J. J. Carbó, J. M. Poblet, R. Neumann, *J. Am. Chem. Soc.* **2014**, *136*, 10941–10948; b) M. M. Hossain, S.-G. Shyu, *Tetrahedron* **2014**, *70*, 251–255.

[5] K. Feng, R.-Y. Zhang, L.-Z. Wu, B. Tu, M.-L. Peng, L.-P. Zhang, D. Zhao, C.-H. Tung, *J. Am. Chem. Soc.* **2006**, *128*, 14685–14690.

[6] R. Lin, F. Chen, N. Jiao, *Org. Lett.* **2012**, *14*, 4158–4161.

[7] G.-Z. Wang, X.-L. Li, J.-J. Dai, H.-J. Xu, *J. Org. Chem.* **2014**, *79*, 7220–7225.

[8] A. Fujiya, A. Kariya, T. Nobuta, N. Tada, T. Miura, A. Itoh, *Synlett* **2014**, *25*, 0884–0888.

[9] X. Baucherel, J. Uziel, S. Jugé, *J. Org. Chem.* **2001**, *66*, 4504–4510.

[10] R. S. Murthy, M. Bio, Y. You, *Tetrahedron Lett.* **2009**, *50*, 1041–1044.

[11] K. Suga, K. Ohkubo, S. Fukuzumi, *J. Phys. Chem. A* **2003**, *107*, 4339–4346.

[12] A. K. Singh, R. Chawla, L. D. S. Yadav, *Tetrahedron Lett.* **2015**, *56*, 653 – 656.

[13] For UV-triggered disulfide homolysis and thiyl addition to olefins, see: a) O. Ito, M. Matsuda, *J. Am. Chem. Soc.* **1979**, *101*, 1815 – 1819; b) O. Ito, M. Matsuda, *J. Am. Chem. Soc.* **1979**, *101*, 5732 – 5735; c) O. Ito, M. Matsuda, *J. Am. Chem. Soc.* **1981**, *103*, 5871 – 5874; d) O. Ito, M. Matsuda, *J. Am. Chem. Soc.* **1982**, *104*, 1701 – 1703.

[14] For a Review on catalysis of radical reactions, see: A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58 – 102; *Angew. Chem.* **2016**, *128*, 58 – 106.

[15] a) A. Yoshimura, Y. Takamachi, L.-B. Han, A. Ogawa, *Chem. Eur. J.* **2015**, *21*, 13930 – 13933; b) X. Pan, J. Lalevée, E. Lacôte, D. P. Curran, *Adv. Synth. Catal.* **2013**, *355*, 3522 – 3526; c) T. Hashimoto, K. Takino, K. Hato, K. Maruoka, *Angew. Chem. Int. Ed.* **2016**, *55*, 8081 – 8085; *Angew. Chem.* **2016**, *128*, 8213 – 8217.

[16] For a Review on thiyl radical chemistry, see: F. Dénès, M. Pichowicz, G. Povie, P. Renaud, *Chem. Rev.* **2014**, *114*, 2587 – 2693.

[17] M. S. Kharasch, W. Nudenberg, G. J. Mantell, *J. Org. Chem.* **1951**, *16*, 524 – 532.

[18] A. Fava, G. Reichenbach, U. Peron, *J. Am. Chem. Soc.* **1967**, *89*, 6696 – 6700.

[19] S. Iriuchijima, K. Maniwa, T. Sakakibara, G.-I. Tsuchihashi, *J. Org. Chem.* **1974**, *39*, 1170 – 1171.

[20] H. H. Szmant, A. J. Mata, A. J. Namis, A. M. Panthananickal, *Tetrahedron* **1976**, *32*, 2665 – 2680.

[21] a) V. T. D'Souza, R. Nanjundiah, J. Baeza, H. H. Szmant, *J. Org. Chem.* **1987**, *52*, 1720 – 1725; b) V. T. D'Souza, V. K. Iyer, H. H. Szmant, *J. Org. Chem.* **1987**, *52*, 1725 – 1728; c) V. T. D'Souza, R. Nanjundiah, J. Baeza, H. H. Szmant, *J. Org. Chem.* **1987**, *52*, 1729 – 1740; d) M.-I. Chung, V. T. D'Souza, H. H. Szmant, *J. Org. Chem.* **1987**, *52*, 1741 – 1744.

[22] R. S. Mulliken, *J. Phys. Chem.* **1952**, *56*, 801 – 822.

[23] R. Foster, *J. Phys. Chem.* **1980**, *84*, 2135 – 2141.

[24] S. V. Rosokha, J. K. Kochi, *Acc. Chem. Res.* **2008**, *41*, 641 – 653.

[25] a) E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre, *Nat. Chem.* **2013**, *5*, 750 – 756; b) E. Arceo, E. Montroni, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 12064 – 12068; *Angew. Chem.* **2014**, *126*, 12260 – 12264; c) M. Nappi, G. Bergonzini, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 4921 – 4925; *Angew. Chem.* **2014**, *126*, 5021 – 5025.

[26] a) W. Liu, J. T. Groves, *Acc. Chem. Res.* **2015**, *48*, 1727 – 1735; b) A. G. M. Barrett, D. J. Rys, *J. Chem. Soc. Chem. Commun.* **1994**, 837 – 838.

[27] W. Adam, S. G. Bosio, N. J. Turro, B. T. Wolff, *J. Org. Chem.* **2004**, *69*, 1704 – 1715.

[28] A previous report by Jugé demonstrated a with sole example that bis(4-chlorophenyl)disulfide (10–50 mol %), in the presence of a Mn-catalyst and UV light from a medium-pressure Hg lamp (250 W) was able to initiate the oxidative cleavage of *trans*-methylstilbene (Ref. [9]). We argue that although the major pathway of Jugé's reaction was initiated with the UV-triggered S−S bond dissociation catalyzed by the Mn complex, a small portion of the reaction might also follow the visible-light mechanism described herein.

[29] H. Otsuka, S. Nagano, Y. Kobashi, T. Maeda, A. Takahara, *Chem. Commun.* **2010**, *46*, 1150 – 1152.

[30] A. M. Belenguer, T. Friščić, G. M. Day, J. K. M. Sanders, *Chem. Sci.* **2011**, *2*, 696 – 700.

[31] A. Rekondo, R. Martin, A. R. de Luzuriaga, G. Cabañero, H. J. Grande, I. Odriozola, *Mater. Horiz.* **2014**, *1*, 237 – 240.

[32] E.-A. I. Heiba, R. M. Dessau, *J. Org. Chem.* **1967**, *32*, 3837 – 3840.

[33] No obvious visible absorption of the olefin–disulfide mixture could be observed with an ordinary UV/Vis spectrometer, presumably because the interaction between disulfide and olefin is transient and not significant enough to be in the detectable range.

[34] J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2016**, *138*, 7402 – 7410.

[35] J. M. Matxain, J. M. Asua, F. Ruipérez, *Phys. Chem. Chem. Phys.* **2016**, *18*, 1758 – 1770.

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Communications

Organocatalysis

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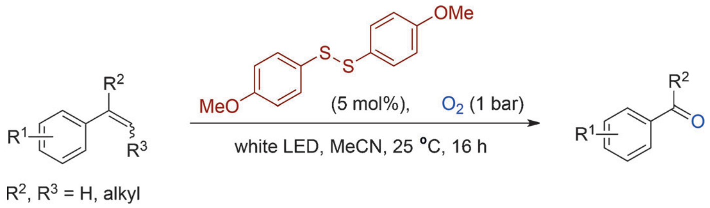
Disulfide-Catalyzed Visible-Light-Mediated Oxidative Cleavage of C=C Bonds and Evidence of an Olefin–Disulfide Charge-Transfer Complex



Mild and metal-free: A photocatalytic method for the aerobic oxidative cleavage of C=C bonds has been developed with electron-rich aromatic disulfides as photocatalyst. Upon visible-light irradiation, aromatic olefins were converted into ketones and aldehydes at ambient temperature. A disulfide–olefin charge-transfer complex is possibly responsible for the S—S bond dissociation.