Purple-Light Promoted Thiol-ene Reaction of Alkenes

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Abstract: Here we present a catalyst-free protocol for the purple light-mediated *anti*-Markovnikov functionalization of alkenes with thiols. Crucial to the generation of the thiyl radical was the formation of a key photo-active complex. More than 30 thioether products were obtained, demonstrating tolerance towards different functional groups and scalability up to 5 mmol of alkene. Two different reaction conditions have been developed, varying both the solvent and the amount of thiol. Depending on the alkene structure, water can be used as an alternative to dichloromethane as a solvent, thus increasing the sustainability of the whole process.

**Keywords:** Alkenes; Ene Reaction; Photochemistry; Radical Reactions; Thiols; Thioethers

Introduction

Thanks to a growing awareness of radical formation and reactivity, photocatalysis has gained momentum in recent years thus becoming a powerful strategy for the construction of complex molecular structures using light as a valuable and renewable energy source.[1] Traditionally, a photocatalyst is required, but the possibility to run a reaction under catalyst- and/or additive-free conditions is even more attractive,[2] allowing not only for mild reaction conditions, but also for the minimization of waste, ease of purification thus reduced manufacturing costs both for academia and industry.

The synthesis of natural products, pharmaceuticals and organic materials are among the fields that could benefit more from the development of alternative catalyst-free, light-driven approaches. In this context, the growing interest in organosulfur compounds, including natural products,[3] drugs,[4] materials,[5] polymers[6] and synthetic intermediates,[7] has led to the search for novel methods for carbon-sulfur bond

formation that overcome the limitations of traditional methodologies (high temperature, toxic solvents, harsh reaction conditions).[8]

Considered a core methodology of modern chemistry, the thiol-ene reaction is a robust transformation allowing new carbon-sulfur bonds in an *anti*-Markovnikov fashion to be formed.[9] The thiol-ene reaction has traditionally been promoted by the thermal or ultraviolet (UV) activation of a radical initiator,[10] recently also under continuous photo-flow regime,[11] or by direct UV irradiation[12] (Scheme 1a). The pioneering works of Yoon[13] and Stephenson[14] demonstrated the ability of metal-based photocatalysts to promote the thiol-ene reaction, thereby driving a definitive transition from UV to visible-light.[15] Since then, there has been a major development in terms of photocatalysts (Scheme 1b), allowing carbon-sulfur bonds to be efficiently formed using both metal-based[16] and organic photocatalysts.[17] Recently, this trend is reversing, and examples of light-mediated, catalyst-free thiol-ene reactions have been published (Scheme 1c). In 2023, Gao *et al.* reported the *anti*-
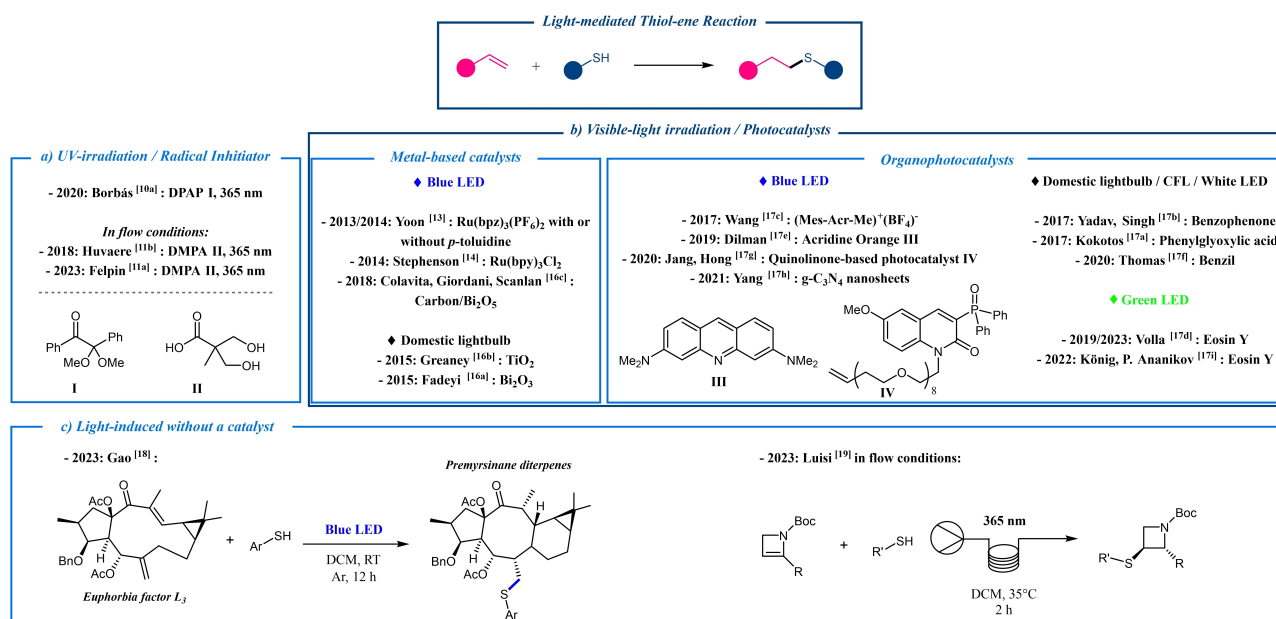
Scheme 1. Summary of the reported protocols for the light-mediated thiol-ene reaction. DPAP: 2,2-dimethoxy-2-phenylacetophenone, DMPA: 2,2-dimethoxy-2-phenylacetophenone, bpz: 2,2′-bipyrazine.

Markovnikov addition of a series of substituted aromatic thiols to the Euphorbia factor L3 under blue light irradiation,[18] while Luisi's group described the addition of thiols to azetines under UV–A irradiation in continuous flow-conditions.[19] Key to the success of these strategies was the generation of the thiyl radical in the absence of any initiator under solely irradiation.[20] Alternatively, as described by Patel,[21] electron-donor-acceptor complex formation can be exploited for the thiyl radical generation.

Achieving high molecular complexity *via* photo-assisted organic transformations in the absence of a photocatalyst may be challenging.[22] Organic reactions driven by visible-light without external photocatalysts are trending at the moment, thus we questioned us on the feasibility of a light-mediated thiol-ene reaction without a catalyst. As part of our ongoing research on the photocatalyzed functionalization of unsaturated compounds,[23] we have developed an operationally simple *anti*-Markovnikov hydrothiolation of alkenes. By fine-tuning the reaction conditions, in particular the choice of solvent mixture, high yields of the desired thioether products were obtained under purple light illumination without a photocatalyst.

Results and Discussion

In order to evaluate the feasibility of a thiol-ene reaction without a photocatalyst or a photosensitizer in the visible-light, we chose hexadec-1-ene **1a** and thiophenol **2a** as the model substrates (Table 1). To our delight, under purple light irradiation (390 nm LED), in the presence of acetic acid and water as additives, at room temperature in CH_2Cl_2 as the solvent, thioether **3a** was obtained in 42% yield (Table 1 entry 1). The light was essential to promote the reaction (Table 1 entry 2), while the presence of acetic acid was not required, indeed product **3a** could be obtained in 77% yield excluding the acid (Table 1 entry 3). The subsequent solvent screening, in the presence of 10 equivalent of H_2O, revealed chlorinated solvents (Table 1 entries 6–9) to be superior to THF (Table 1 entry 4) and CH_3CN (Table 1 entry 5). The exclusion of O_2 from the reaction mixture was the key for improving the yields, hinting to a radical mechanism. A marked inhibitory effect of O_2 was observed in $CHCl_3$, with an increase in yield from 32 to 79% when switching from the non-degassed to the degassed solvent. (Table 1 entries 6–7). The removal of O_2 from CH_2Cl_2 allowed an improved 86% yield (Table 1 entry 8) to be reached. The employment of H_2O, not only as an additive, but as the solvent was beneficial to the reaction allowing thioether **3a** to be obtained in 98% yield (Table 1 entry 10). A control experiment in the dark revealed the presence of a background reaction in H_2O contributing to a 45% yield of **3a** (Table 1 entry 11). Although the presence of a background reaction, purple light was able to boost the thiol-ene reaction to a quantitative production of the *anti*-Markovnikov compound **3a**. The use of H_2O as the solvent in combination with light-irradiation is surely attractive and in agreement with the green chemistry principles.[24] Moreover, on water conditions were identified where the lipophilic substrates form an

Table 1. Optimization of reaction conditions.[a]
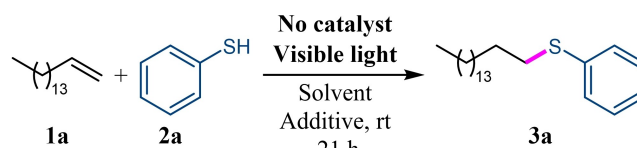
Entry	λ [nm]	Solvent[b]	Additive [4.5 eq]	H$_2$O [eq]	2a [eq]	Yield [%][d]
1	390 nm (52 W)	CH$_2$Cl$_2$	CH$_3$CO$_2$H	10	1.6	42
2	–	CH$_2$Cl$_2$	CH$_3$CO$_2$H	10	1.6	N.D.
3	390 nm (52 W)	CH$_2$Cl$_2$	–	10	1.6	77
4	390 nm (52 W)	THF	–	10	1.6	11
5	390 nm (52 W)	CH$_3$CN	–	10	1.6	25
6	390 nm (52 W)	CHCl$_3$	–	10	1.6	32
7	390 nm (52 W)	CHCl$_3$ c)	–	10	1.6	79
8	390 nm (52 W)	CH$_2$Cl$_2$ c)	–	10	1.6	86
9	390 nm (52 W)	CH$_3$CN c)	–	10	1.6	50
10	390 nm (52 W)	H$_2$O c)	–	–	1.6	**98**
11	–	H$_2$O c)	–	–	1.6	45

Screening of reaction conditions in CH$_2$Cl$_2$ as the solvent

Entry	λ [nm]	Conc. [M][c]	H$_2$O [eq]	2a [eq]	Yield [%][d]
12	370 nm (43 W)	0.2 M	10	1.6	83
13	456 nm (50 W)	0.2 M	10	1.6	22
14	White LED	0.2 M	10	1.6	65
15	390 nm (52 W)	0.4 M	10	1.6	80
16	390 nm (52 W)	0.1 M	10	1.6	47
17	390 nm (52 W)	0.2 M	5	1.6	85
18	390 nm (52 W)	0.2 M	10	2.5	**>99**

[a] Reaction condition: hexadec-1-ene **1 a** (1 mmol), thiophenol **2 a** (1.6 or 2.5 mmol), H$_2$O (5 or 10 mmol), CH$_3$CO$_2$H (4.5 eq) as an additive, in the reported solvent (5 ml) under illumination with a Kessil LED lamp, 21 h, room temperature.
[b] The reaction was performed in 5 ml of the reported solvent.
[c] The reaction mixture was degassed applying 3 freeze-pump-thaw cycles.
[d] Yield determined by NMR with CH$_3$NO$_2$ as the internal standard.

emulsion after vigorous stirring and freeze-pump-thaw cycles.[25]

Considering the good result obtained in degassed CH$_2$Cl$_2$, a deeper screening of the reaction conditions was conducted, thus the effect of the light wavelength, the concentration, the amount of water and thiophenol **2 a** were evaluated in this solvent. Unsatisfactory results were obtained at 456 nm (22% yield, Table 1 entry 13) and with a white LED (65% yield, Table 1 entry 14). Comparable results to 390 nm irradiation were achieved at 370 nm (83% yield, Table 1 entry 12), even though we considered more convenient the employment of purple light instead of UV–A radiation. A dilution of the reaction mixture from 0.2 M to 0.1 M in CH$_2$Cl$_2$ was not beneficial, resulting in a poor 47% yield of **3 a** (Table 1 entry 16). A small decrease in yield was obtained either in a more concentrated solution (0.4 M, Table 1 entry 15) or reducing the amount of H$_2$O to 5 equivalents (Table 1 entry 17). Finally increasing the equivalents of thio-

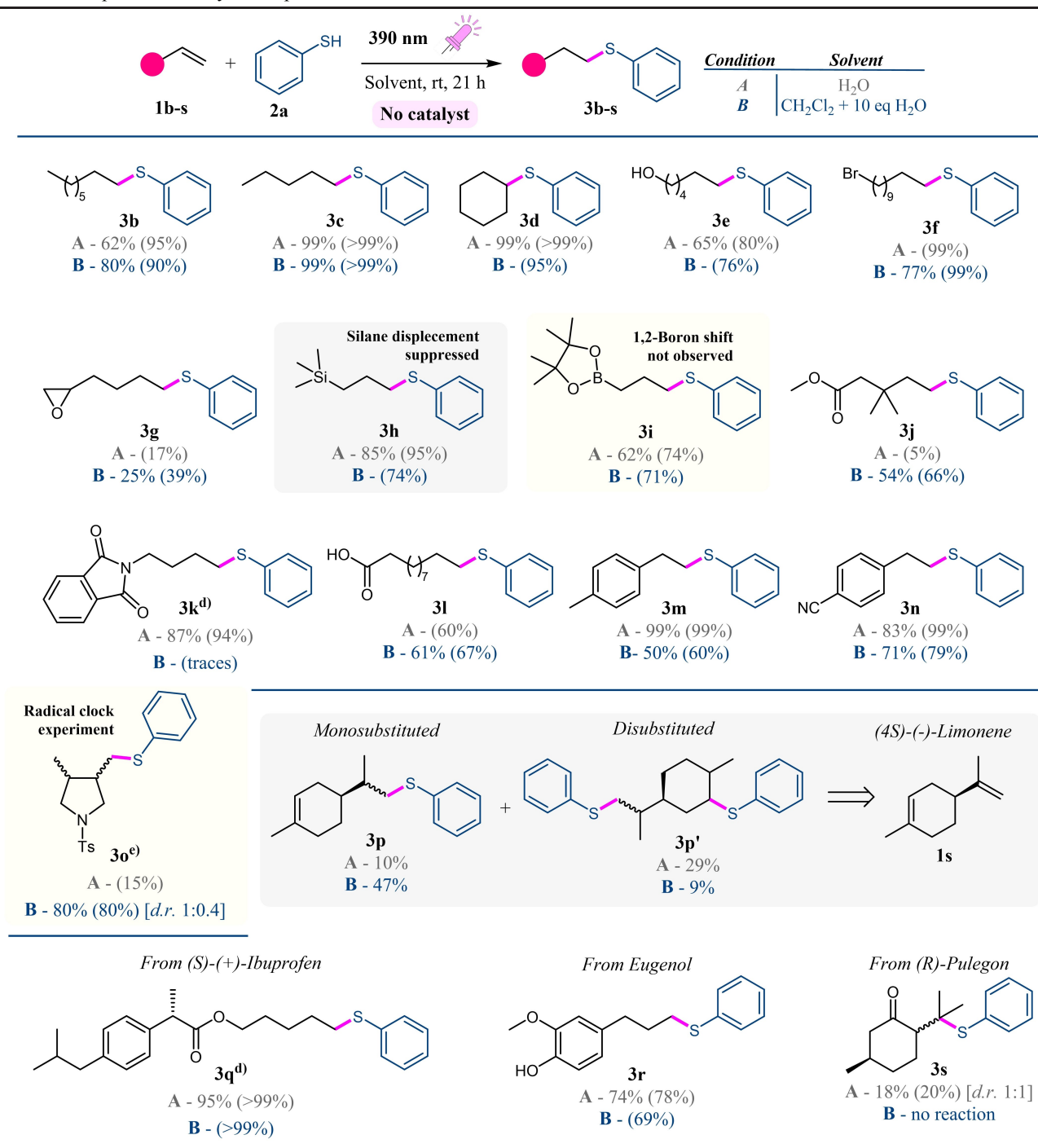phenol **2 a** to 2.5 allowed a quantitative yield for **3 a** to be obtained (Table 1 entry 18).

As can be seen from Table 1 entries 10 and 18, two different conditions were found to be optimal allowing for the isolation of **3 a** in almost quantitative yields, at room temperature, under irradiation from a purple LED and without any photocatalyst or photosensitizer. Thus, two simple setups, composed either of 1.6 equivalents of thiophenol **2 a** in degassed H$_2$O as the solvent (identified as condition A in the reaction scope) or 2.5 equivalents of thiophenol **2 a** in the presence of 10 equivalents of H$_2$O as an additive in degassed CH$_2$Cl$_2$ (identified condition B in the reaction scope), enabled the efficient *anti*-Markovnikov functionalization of alkene **1 a** to afford thioether **3 a**. Both conditions were applied in the extension of the reaction scope.

Scope of the Reaction

With two different optimized conditions in hand, we proved the wide applicability of this catalyst-free protocol testing diverse alkenes (**1a**–**u**) and thiols (**2a**–**l**). As shown in Table 2 and Table 3 a high tolerance towards functional groups was demonstrated with yields from good to excellent in both H_2O and CH_2Cl_2 as the solvents. Reactions were carried out on 1 mmol scale except for alkenes **1k**, **1o** and **1q**. Moreover, the model reaction between hexadec-1-ene **1a** and thiophenol **2a** was scaled-up to 5 mmol of alkene with a marginal difference on the outcome for **3a** yield (condition A in H_2O 86% yield on 5 mmol vs 98% on 1 mmol; condition B in CH_2Cl_2 89% yield on 5 mmol vs 99% on 1 mmol). Olefins with different chain lenghts were tested with **2a**. Oct-1-ene **1b** afforded **3b** in 62% isolated yield in H_2O and 80% isolated yield was obtained in CH_2Cl_2. Higher yields were achieved with pent-1-ene **1c** in both conditions (99% isolated yield). Thioether **3d** was obtained in yield equal or higher than 95% in both conditions, employing cyclohexene **1d** as the starting material. In a previous paper,[26] Ranu and Mandal reported the synthesis of **3d** in 70% yield *via* a hydrothiolation reaction in H_2O without light. Althought the reactivity reported for cyclohexene **1d** in H_2O,[26] we were not able to reproduce these data in the dark, obtaining only 17% yield for **3d** in H_2O and no product formation was detected in CH_2Cl_2, emphasising the need for light irradiation to achieve high conversions. Good leaving groups as well as protic groups (e.g. Br and OH) were tolerated as demonstrated in the case of hex-5-en-1-ol **1e** and 11-bromoundec-1-ene **1f**, whose corresponding thioethers were obtained in good yields. The epoxy ring derived from 2-(but-3-en-1-yl)oxirane **1g** could be introduced even though yields lower than 30% were observed in both solvents because of degradation of the starting material. With allyltrimethylsilane **1h** and allyl boronic acid pinacol ester **1i**, either silane displacement or 1,2-boron migration was not detected, allowing the corresponding thioethers **3h** and **3i** to be recovered from good to high yields. Superior results were obtained for silylated alkene **1h** on H_2O than in CH_2Cl_2/H_2O, while boronated **1i** gave comparable results in the two conditions. Opposed outcomes were attained in the presence of an ester or a masked amine functionality. Alkene **1j**, bearing an ester moiety, in fact, gave good yields in CH_2Cl_2 and traces of product **3j** in H_2O; while 4-phthalamido-but-1-ene **1k** gave 87% isolated yield in H_2O and traces of **3k** in the organic solvent. Carboxylic acid **1l** was well tolerated in both conditions. The protocol was also extended to styrenes **1m** and **1n**, giving better results in H_2O than in CH_2Cl_2/H_2O. Higher yields were obtained with 4-cyanostyrene **1n** demonstrating an increased reactivity for electron-poor styrenes in the presence of the thiyl

radical. A radical cascade reaction initiated by light and the thiyl radical was exploited for the synthesis of pyrrolidine **3o** from *N*-tosyl diallyl amine **1o**.

The *N*-containing heterocycle **3o** was obtained as a mixture of diasteroisomers (d.r. 1/0.4) in 80% yield applying condition B, while it was recovered in a very low yield (15%) in H_2O. Finally, the catalyst-free thiol-ene reaction mediated by purple light was validated on natural and biological active molecules. Differently from our hydrosulfonylation reaction,[23d] the addition of thiophenol **2a** to (4*S*)-(−)-limonene **1p** afforded a mixture of monosubstituted **3p** and disubstituted **3p'** products. When employing H_2O as the solvent, disubstituted **3p'** was preferentially formed over the monosubstituted compound (1:2.9 ratio for **3p**:**3p'**). Switching to CH_2Cl_2, and employing H_2O only as an additive, it was possible to tune the thiophenol **2a** addition directing it preferentially to the terminal double bond. In this case the mosubstituted thioether **3p** was obtained in 47% yield, with only a 9% of **3p'**. Hydrothiolated analogous of (*S*)-(+)-Ibuprofen derivative **1q** and eugenol **1r** gave comparable results in both conditions. Thioether **3q**, derived from Ibuprofen **1q**, was formed in almost quantitative yields (condition A: 95%; condition B 99%), whereas the sterically hindered thioether **3s** as a 1:1 mixture of diasteroisomers, only in water, with a low yield of 18%. Longer reaction times (up to 42 h), did not increase the yield due to the reduced reactivity of the tetrasubstituted double bond of (*R*)-pulegon **1s**. The scope of thiols was next studied applying both aromatic and aliphatic thiols as shown in Table 3. The effect of groups with different electronic properties was firstly evaluated. 4-Methoxythiophenol **2b** showed an increased reactivity in H_2O than in CH_2Cl_2 (99% vs 68% yield) with alkene **1a**. When the methoxy group was moved to the *ortho*-position (**2c**), a drop in yields was observed in both conditions (A: 33%; B: 36% yields), probably due to the increased steric hindrance. The reaction between 4-chlorothiophenol **2d** and **1a** proceeded in high yields in both conditions A and B, while when **2c** was reacted with allyl boronic acid pinacol ester **1i** only 41% yield was obtained in H_2O. The yield could be easily raised up to 77% applying condition B. The reactivity of 2-naphthalene-thiol **2e**, furfuryl mercaptan **2f** and benzyl mercaptan **2g** was then evaluated reacting them respectively with pent-1-ene **1c**, allyltrimethylsilane **1h** and 11-bromoundec-1-ene **1f**, showing results comparable to those of thiophenol **2a** (Table 3). Finally, aliphatic thiols were tested. 1-Dodecanethiol **2h** was reacted with allyl alcohol **1t**. Although a quantitative yield could be determined by NMR, product **4h** was isolated only in 50% yield. In general, we observed an increased volatility which could affect the isolated yields, reducing those calculated by NMR, for thioethers derived from aliphatic thiols. The reaction

Table 2. Scope of the catalyst-free photo-induced thiol-ene reaction in the alkene.[a,b,c]

Condition	Solvent
A	H$_2$O
B	CH$_2$Cl$_2$ + 10 eq H$_2$O

3b
A - 62% (95%)
B - 80% (90%)

3c
A - 99% (>99%)
B - 99% (>99%)

3d
A - 99% (>99%)
B - (95%)

3e
A - 65% (80%)
B - (76%)

3f
A - (99%)
B - 77% (99%)

3g
A - (17%)
B - 25% (39%)

Silane displacement suppressed
3h
A - 85% (95%)
B - (74%)

1,2-Boron shift not observed
3i
A - 62% (74%)
B - (71%)

3j
A - (5%)
B - 54% (66%)

3k[d]
A - 87% (94%)
B - (traces)

3l
A - (60%)
B - 61% (67%)

3m
A - 99% (99%)
B- 50% (60%)

3n
A - 83% (99%)
B - 71% (79%)

Radical clock experiment
3o[e]
A - (15%)
B - 80% (80%) [*d.r.* 1:0.4]

Monosubstituted
3p
A - 10%
B - 47%

Disubstituted
3p'
A - 29%
B - 9%

(4S)-(-)-Limonene
1s

From (S)-(+)-Ibuprofen
3q[d]
A - 95% (>99%)
B - (>99%)

From Eugenol
3r
A - 74% (78%)
B - (69%)

From (R)-Pulegon
3s
A - 18% (20%) [*d.r.* 1:1]
B - no reaction

[a] Reaction conditions A: Alkene **1a–s** (1 mmol), thiophenol **2a** (1.6 eq.), in H$_2$O (5 mL, 0.2 M), 52 W Kessil purple LED lamp (390 nm), 21 h, room temperature. Reaction conditions B: Alkene **1a–s** (1 mmol), thiophenol **2a** (2.5 eq.), H$_2$O (10 eq.) in CH$_2$Cl$_2$ (5 mL, 0.2 M), 52 W Kessil purple LED lamp (390 nm), 21 h, room temperature.
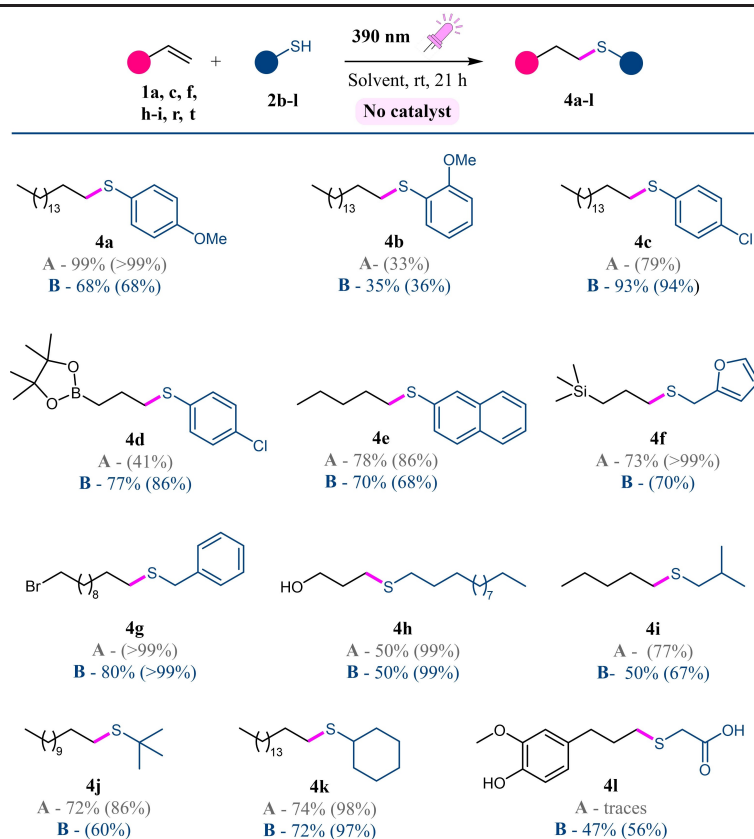[b] Yield determined on the isolated product; in brackets () yields determined by NMR with CH$_3$NO$_2$ as the internal standard.
[c] The reaction mixture was degassed applying 3 freeze-pump-thaw cycles.
[d] Reaction carried out on 0.2 mmol of **1k** and **1q**.
[e] Reaction carried out on 0.5 mmol of **1o**.

between pent-1-ene **1c** and 2-methyl-1-propanethiol **2i** furnished thioether **4i** from good to high yields in both

conditions. *Tert*-butyl mercaptan **2j** and cyclohexane-thiol **2k** reacted respectively with dodec-1-ene **1u** and

Table 3. Scope of the catalyst-free photo-induced thiol-ene reaction in the thiol.[a,b,c]

[a] Reaction conditions A: Alkene **1 a**, **c**, **f**, **h–i**, **r**, **t** (1 mmol), thiol **2 b–l** (1.6 eq.), in H_2O (5 mL, 0.2 M), 52 W Kessil purple LED lamp (390 nm), 21 h, room temperature. Reaction conditions B: **1 a**, **c**, **f**, **h–i**, **r**, **t** (1 mmol), thiol **2 b–l** (2.5 eq.), H_2O (10 eq.) in CH_2Cl_2 (5 mL, 0.2 M), 52 W Kessil purple LED lamp (390 nm), 21 h, room temperature.
[b] Yield determined on the isolated product; in brackets () yields determined by NMR with CH_3NO_2 as the internal standard.
[c] The reaction mixture was degassed applying 3 freeze-pump-thaw cycles.

hexadec-1-ene **1 a** producing the corresponding thio-ether **4 j** and **4 k** in comparable yields both in the aqueous and the organic solvent. Thioglycolic acid **2 l** did not react with eugenol **1 r** in H_2O, while applying condition B thioether **4 l** was isolated in 47% yield.
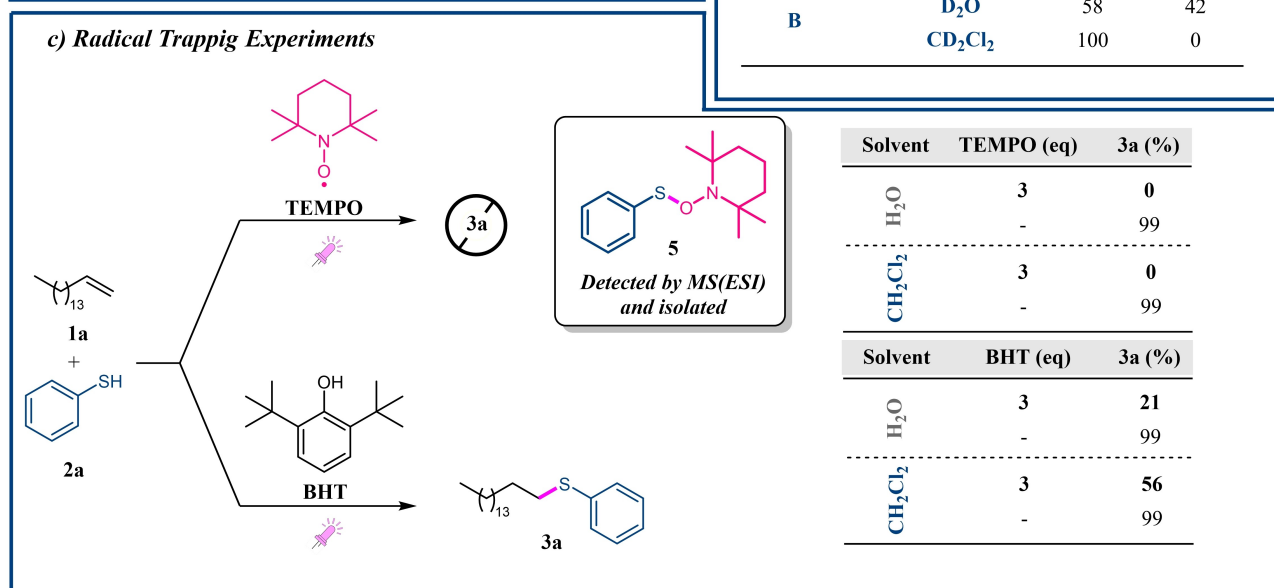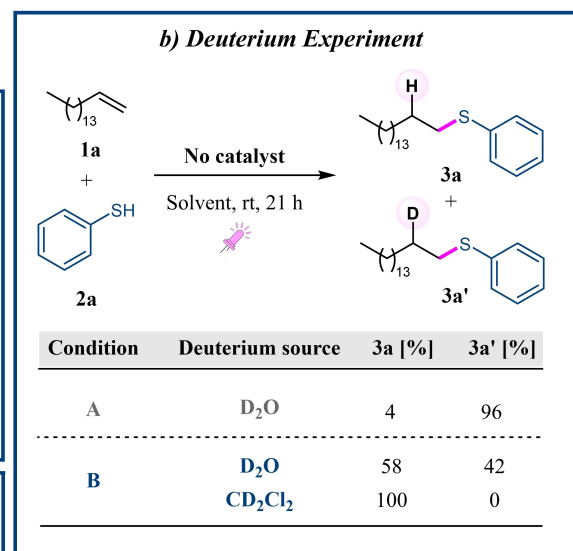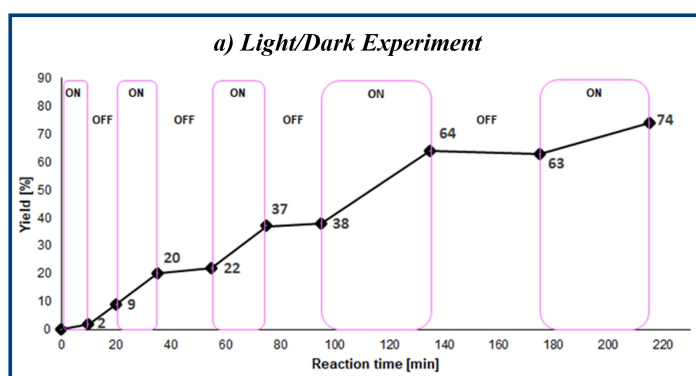
Mechanistic Studies: Experimental and Computational

Experimental Mechanistic Studies

In order to unveil the mechanism of this thiol-ene reaction mediated by purple light, we turned our attention to mechanistic studies (Scheme 2). A light-dark experiment together with the control experiment reported in Table 1, entry 2 demonstrated the crucial role of the light in promoting the thiol **2 a** addition to the alkene **1 a** in CH_2Cl_2. As shown in Scheme 2a, the reaction progressed solely under continuous irradiation, except for the initial 55 minutes (corresponding to two cycles of light on and two cycles of light off)

where product **3 a** formation was observed also in the dark. This observation can agree with a not efficient radical chain mechanism, since the background reaction in CH_2Cl_2 was excluded by the control experiment in the dark. Unfortunately, the same experiment was not feasible in H_2O (condition A), because the precipitation of thioether **3 a** during the reaction progression could misrepresent the collected data. Anyway, the precipitation of solid thioethers could be exploited in favor of simpler and greener product purification avoiding column chromatography.

Having a clue for a radical mechanism by the reduced reaction efficiency in the presence of molecular O_2 (Table 1 entries 3–6), we confirmed the formation of radical intermediates performing trapping experiments with the radical scavengers TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and BHT (2,6-di-*tert*-butyl-4-methylphenol) (Scheme 2c). In the presence of 3 equivalents of BHT, the yield of the thiolated product **3 a** dropped to 56% in CH_2Cl_2 (standard condition B). In H_2O (standard condition A), the yield

a) Light/Dark Experiment

b) Deuterium Experiment

Condition	Deuterium source	3a [%]	3a' [%]
A	D_2O	4	96
B	D_2O	58	42
	CD_2Cl_2	100	0

c) Radical Trappig Experiments

5
*Detected by MS(ESI)
and isolated*

Solvent	TEMPO (eq)	3a (%)
H_2O	3	0
	-	99
CH_2Cl_2	3	0
	-	99

| Solvent	BHT (eq)	3a (%)
H_2O	3	21
	-	99
CH_2Cl_2	3	56
	-	99

Scheme 2. a) The light/dark experiment. b) The deuterium experiment. c) The TEMPO/BHT trapping experiment. The details of the experimental conditions for each study are reported in the SI.

of **3a** further dropped to 21%. In both cases, any BHT-adduct could be found. On the contrary, when 3 equivalents of TEMPO were added to the reaction mixture under both conditions A and B, the formation of thioether **3a** was completely suppressed and the TEMPO-thiyl adduct **5** was detected by MS(ESI) analysis of the crude reaction mixture. Interestingly, the TEMPO-thiyl adduct **5** was found also when thiophenol **2a** was irradiated under purple light in the presence of TEMPO without the alkene **1a**, suggesting the possibility for the photolysis of **2a** at 390 nm, although no absorption for thiophenol **2a** was observed at this wavelength. Radical involvement was further confirmed by the radical clock experiment performed with *N*-tosyl diallyl amine **1o**, delivering the radical addition/cyclization cascade product **3o** (Table 2), thus demonstrating the partecipation of radical **3c•** (Scheme 3).

Deuterium experiments showed the introduction of deuterium at the β-position of thioether **3a** (Scheme 2b). Deuterated CD_2Cl_2 was not able to donate the deuterium, while the deuterated product **3a'** was obtained along with the non-deuterated **3a** in 42:58 ratio in the presence of 10 equivalents of D_2O. When D_2O was employed as the solvent an almost complete deuteration was observed with a 96:4 (**3a'**: **3a**) ratio.

Computational Mechanistic Study

Computational studies were performed on pent-1-ene **1c** as the model alkene and thiophenol **2a**. All the details on the method are reported in Section 1 of the Supplementary Information - Computational Data file.
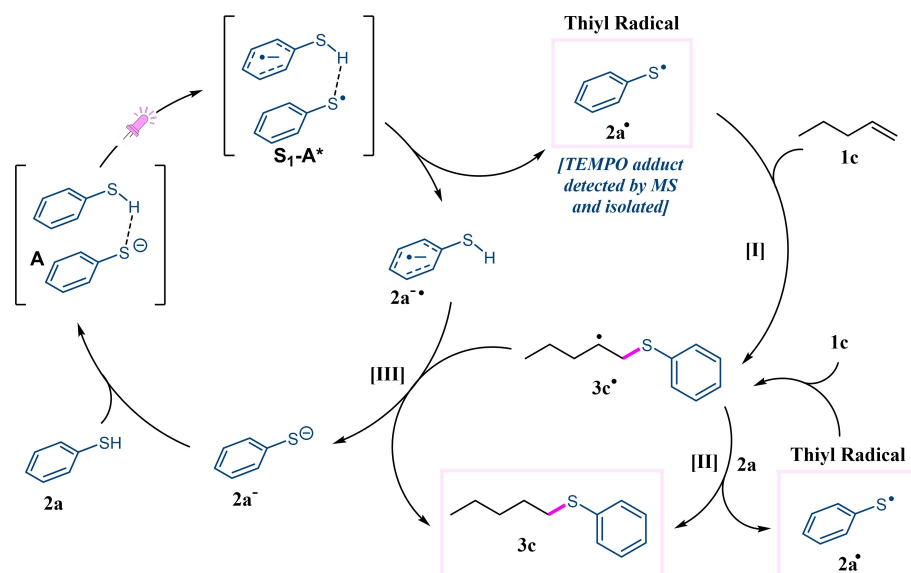
Scheme 3. The proposed radical reaction mechanism for the photolytic *anti*-Markovnikov addition of thiophenol **2 a** to 1-pentene **1 c** as the model alkene.

Radical Generation

At a first glance the phenylthiyl radical (C$_6$H$_5$S$^\bullet$, **2 a$^\bullet$**) should be the starting species. However, its generation by direct photolysis of the S–H bond in the thiophenol **2 a** cannot take place in the visible region. Deeper UV wavelenght are, generally, required (Table S-TD-1 Section 4.1 in the SI-CD and references[9b,27]), although substitutions or heteroatoms can exercitate a bathochromic effect. Therefore, we were quite surprised to find out that the thiol-ene reaction between alkene **1 a** and thiol **2 a** could take place also under blue-light irradiation (Table 1 entry 13).

Recently, Miyake[28] and Xia[29] reported the generation of an aryl-thiyl radical *via* the photo-induced electron-transfer within the two components of a complex formed between a thiophenolate anion and iodobenzene. The aryl-thiyl radical, thus generated, was then exploited in visible-light promoted carbon-sulfur cross-coupling reactions. In a similar way, we suggest the formation of the key photo-active complex **A** between thiophenol **2 a** and thiophenolate **2 a$^-$** (Figure 1, **left**). Considering that the pK$_a$ of thiophenol is around 6.5 – 9 depending on the solvent,[30][31], small amounts of thiophenolate **2 a$^-$** should be available in our reaction conditions. Our calculation estimated for complex **A** a free energy of only 0.7 kcal mol^{-1} above the separated species, therefore considering the large excess of thiophenol **2 a** employed in both reaction conditions, some amounts of complex **A** should be present (Reaction [1] in section 3, Table S-1 and Section 5.1 in the SI-CD).

Once complex **A** is formed, the absorption of light leads to an electron transfer from the thiophenolate
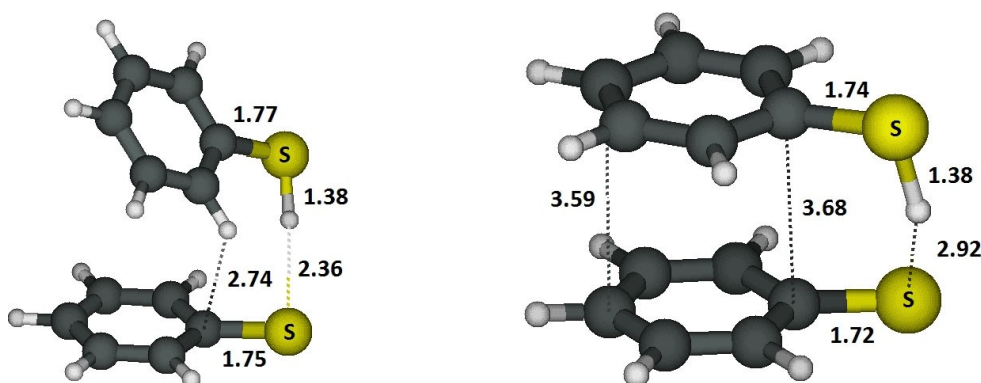
Figure 1. The structure of the photo-active complex **A** formed by thiophenol **2 a** and thiophenolate **2 a$^-$** (left), the structure of it first excited state **S$_1$-A*** (right).

2 a⁻ to the thiophenol **2 a** generating the new complex **S₁-A***, consisting of a phenylthiyl radical and a thiophenol radical anion, whose dissociation in the two separated species is thermodynamically favoured by 4.4 kcal mol⁻¹ in term of free energy (Figure 1, **right**). As shown in Scheme 3, both species are involved in the mechanism proposed by us. A complete discussion of the computational data collected about the phenyl-thiyl radical generation is reported in the Section 2 of the SI-CD (Tables S-1a/b and Section 5.1 in the SI-CD).

Radical Reactions

The proposed radical reaction mechanism for the photolytic *anti*-Markovnikov addition of thiophenol **2 a** to pent-1-ene **1 c** is shown in Scheme 3. The whole reaction is thermodynamically favoured by 9.4 kcal mol⁻¹ in term of free energy (Table S-2 and Section 5.2 in the SI-CD). The *anti*-Markovnikov addition of the phenylthiyl radical **2 a**• to the C^1 of the model alkene **1 c** is very fast (pathway [**I**] in Scheme 3 and in Section 3 of the SI-CD). The calculated rate constant k_1 is $7.8 \cdot 10^6$ M⁻¹ s⁻¹, but the radical intermediate **3 c**• is less stable than the reactant by 5 kcal mol⁻¹ in term of free energy (Table S-2) making this step reversible. These data are in full agreement with that reported in the Dénès review.[9b] In any case, the addition to the C^2 of **1 c**, leading to the Markovnokov product, is slower (reaction [1′] in the SI-CD, $k_{1'} = 2 \cdot 10^4$ M⁻¹ s⁻¹) and even less thermodi-namically favoured ($\Delta G = 8.1$ kcal mol⁻¹). At that point, the reaction can proceed by propagation or termination.

The propagation reaction (Scheme 3 path [**II**]) involves a Hydrogen-Atom-Tranfer (HAT) from thio-phenol **2 a** to the radical **3 c**•. This step is extremely fast ($k_2 = 3.3 \cdot 10^8$ M⁻¹ s⁻¹) and exoergic ($\Delta G = -14.8$ kcal mol⁻¹). It regenerates the phenylthiyl radical **2 a**• preventing the polymerization along with relatively high concentration of the thiol,[32] in agreement with the literature.[9b] A termination reaction between the radical **3 c**• and thiophenol radical anion **2 a**•⁻, generated along with the phenylthiyl radical **2 a**•, allowed the formation of the product **3 c**. Because this reaction involves two radicals the whole spin status depends on how the single spins are coupled. In the case of a triplet status, the HAT reaction shown in path [**III**] of Scheme 3 is very fast ($k_3 = 4.2 \cdot 10^8$ M⁻¹ s⁻¹) and exoergic ($\Delta G = -18.9$ kcal mol⁻¹), it yields the final thioether **3 c** regenerating the anion **2 a**⁻ thus closing the whole reaction cycle. Indeed, the thiophenolate **2 a**⁻ is generated in its triplet state, but its decay to the singlet ground state is expected to be fast and easy. Although, it was not possible to easily study this HAT reaction in the singlet state because this would correspond to an excited state (the singlet ground state

of an ensemble on **3 c**• and **2 a**•⁻ spontaneously decay to the carbanion and to the radical **2 a**•), we expected the HAT yielding **2 a** and **3 c** to be very fast being the reaction even more exoergic ($\Delta G = -80.6$ kcal mol⁻¹).

The radical **3 c**• can give other three HAT reactions that we believed to be worthwhile to consider: those from the solvents CH_2Cl_2 and H_2O and that from the alkene **1 c**. Considering the reaction from CH_2Cl_2 to be monomolecular, being the solvent already in contact with the radicals (reaction [4] in SI-CD), this HAT is very slow ($k_4 = 30$ s⁻¹) and barely exoergic ($\Delta G = -3.0$ kcal mol⁻¹).

Although the concentration of **2 a** is more than 30 times lower than that of CH_2Cl_2, but the rate of the HAT reaction from **2 a** to **3 c**• is 10^7 times faster, the reaction with the solvent is negigible. This is in agreement with the lack of deuteration employing CD_2Cl_2 as the solvent. The HAT reaction with H_2O (reaction [4′] in SI-CD) is definetely endoergic ($\Delta G = 25.1$ kcal mol⁻¹), but as demonstrated by the deuterium experiments the exchange with the acidic proton of the phenylthiol takes place during the process.

The HAT from the alkene **1 c** (reaction [5] in SI-CD), although being exoergic ($\Delta G = -11.5$ kcal mol⁻¹), is too slow ($k_5 = 4.6$ M⁻¹ s⁻¹) to compete with that of thiophenol **2 a**, having a concentration in the same order of **1 c**.

Ionic Reactions

An additional evidence against an ionic mechanism is the lack for Markovnikov product formation (reactions [6] and [6′] in SI-CD). The calculation performed to confirm this conclusion revealed the rate constant for the ionic addition of **2 a** to **1 c** to be very small (Table S-3 and Section 5.3 in the SI-CD). Moreover, in case of ionic reaction only the Markovnikov product should be found being its rate constant 10^7 greater than that for the the *anti*-Markovnikov addition.

Conclusion

In summary, we have developed a general light-mediated hydrothiolation of unactivated alkenes with aromatic and aliphatic thiols under catalyst-free con-ditions. The methodology allows access to more than 30 thioethers containing several reactive functional-ities, such as epoxides, alcohols or halides, with scalability up to 5 mmol both in H_2O and in a CH_2Cl_2/H_2O mixture as the solvent. Natural products and biologically active molecules can be functionalized with thiols as well. Experimental and computational mechanistic studies revealed that the key thiyl radical can be formed by an innovative mechanism involving a photoactive adduct derived from the thiol and its anion upon interaction with light. Thanks to a fine tuning of the solvent mixture the thiyl radical

formation can be realized without the need for a catalyst.

Experimental Section

General Procedures for the Light Mediated Synthesis of Thioethers

Procedure A: A Schlenk tube, equipped with a magnetic stirring bar, was charged with the alkene **1 a–u** (1 mmol, 1 eq) and a thiol **2 a–l** (1.6 mmol, 1.6 eq). Then 5 ml of H_2O were added. The reaction mixture was sealed with a septum and left under stirring for some minutes, then degassed through 3 freeze-pump-thaw cycles. After the last cycle, the reaction was back-filled with N_2. The Schlenk tube was, subsequently, placed at 4 cm from a Kessil purple lamp (390 nm, 52 W) and left under stirring while illuminated at room temperature for 21 h. After this time, the reaction mixture was diluted with 15 ml of EtOAc and the organic phase was washed with NaOH 0.2 M (1x10 ml). The two phases were separated and the aqueous layer was extracted with EtOAc (3x15 ml). The combined organic phases were dried over Na_2SO_4. After the removal of the solvent under reduced pressure, the thioether **3 a–s** or **4 a–l** was purified by column chromatography on silica gel.

Procedure B: A Schlenk tube, equipped with a magnetic stirring bar, was charged with the alkene **1 a–u** (1 mmol, 1 eq) and a thiol **2 a–l** (2.5 mmol, 2.5 eq), then 5 ml of CH_2Cl_2 were added followed by H_2O (180 mg, 10 mmol, 10 eq). The reaction mixture was sealed with a septum and left under stirring for some minutes, then degassed through 3 freeze-pump-thaw cycles. After the last cycle, the reaction was back-filled with N_2. The Schlenk tube was, subsequently, placed at 4 cm from a Kessil purple lamp (390 nm, 52 W) and left under stirring while illuminated at room temperature for 21 h. After this time, the reaction mixture was diluted with 15 ml of CH_2Cl_2 and the organic phase was washed with NaOH 0.2 M (1x10 ml). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3x15 ml). The combined organic phases were dried over Na_2SO_4. After the removal of the solvent, the product **3 a–s** or **4 a–l** was purified by column chromatography on silica gel.

Acknowledgements

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