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A sunlight-compatible photochemical thiol–ene reaction promoted by a paracyclophane-derived photocatalyst

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A sustainable thiol–ene (yne) click reaction has been developed using a paracyclophane derived photocatalyst (1–2.5 mol%) in ethanol under @LED405 or sunlight at room temperature. This methodology features simple conditions and broad scope and tolerates different functional groups either on an olefin or thiol. Experimental probes demonstrate the radical character of the reaction and the quantum yield measurements suggest a close catalytic radical cycle over a chain mechanism.

Green foundation

1. Our work advances the field of green chemistry by reporting the synthesis and application of a new family of paracyclophane-derived photocatalysts that are compatible with sunlight irradiation. These photocatalysts enable efficient thiol–ene (yne) click reactions under mild conditions, reducing energy input and promoting more sustainable synthetic processes.

2. Our specific green chemistry achievement lies in the development of a thiol–ene (yne) reaction under environmentally benign conditions. The transformation proceeds in ethanol as a green solvent, at room temperature, under 405 nm LEDs or natural sunlight. The methodology is operationally simple, exhibits a broad substrate scope, and tolerates a wide range of functional groups. Importantly, the photocatalyst is effective at very low loadings (1 to 2.5 mol%), and its low toxicity was demonstrated, supporting its potential for sustainable and safer chemical processes.

3. It will be beneficial to expand the application of this new family of photocatalysts to areas such as polymer science, surface modification, and bioconjugation, where light-driven, metal-free processes are particularly attractive. For example, their use in a key step in dendrimer synthesis highlights their potential to enable more efficient, modular, and sustainable synthetic strategies.

Thiol–ene reactions have long[1] been recognized for their efficiency, atom economy, and functional group tolerance, making them indispensable in polymer science, surface modification, and bioconjugation.[2] Their operational simplicity and broad applicability have led to their widespread use in fields ranging from protective coatings[3] and cross-linked materials[4] to drug delivery, biosensing, and peptide chemistry.[5] However, conventional thiol–ene protocols often rely on toxic radical initiators,[6] transition-metal complexes,[7] or high-energy UV irradiation.[8] These features raise concerns regarding safety, scalability, and environmental impact (Fig. 1).

The growing demand for "greener" radical processes has positioned photocatalysis as a powerful approach to radical-mediated thiol–ene transformations, offering mild reaction conditions, short reaction times, and compatibility with visible light.[9–12] Metal-free organic photocatalysts that promote direct hydrogen atom transfer (HAT)[13]— in particular aromatic

ketones[14] and aldehydes[15]—have gained prominence due to their ease of synthesis and tunable photophysical properties, and inherently metal-free character. Benzophenone, acetophenone and related derivatives have shown broad applicability in light-driven thiol–ene couplings,[16] achieving notable success in polymer crosslinking[17] and surface grafting.[18] Their photo-
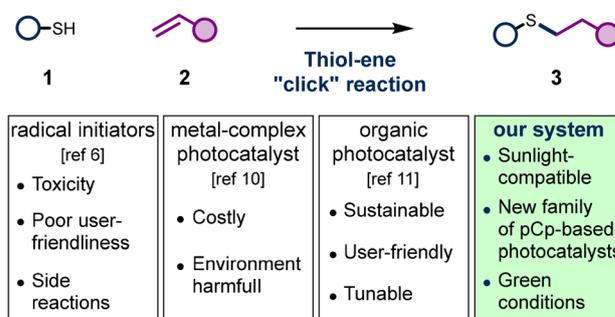

Fig. 1 Main existing strategies for radical-based thiol–ene "click" reactions *vs.* our system.

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sensitization reactivity is comparable to that of metal-based systems, while avoiding issues of toxicity, scarcity and end-of-life contamination, thereby aligning more directly with the core principles of green chemistry. However, despite these advances, the development of organic photocatalysts that combine efficiency, sustainability, low toxicity and structural versatility remains an ongoing challenge.

Our group recently demonstrated that benzylic radicals within [2.2]-paracyclophane (pCp) frameworks exhibit enhanced stabilization *via* through-space delocalization between the cofacial aromatic rings.[19] This unique electronic architecture imparts enhanced lifetimes and reactivity to radical intermediates, offering a promising scaffold for photocatalyst design. In this study, we report the development of a novel paracyclophane-based family of ketones that functions as an efficient photocatalyst for thiol–ene coupling. The reaction proceeds under visible light or sunlight irradiation, employs ethanol as a green solvent, and requires only 2.5 mol% catalyst loading. These features position our system as a practical and sustainable alternative for radical-mediated thiol–ene reactions.

We initiated the investigation of radical thiol–ene reaction enabled by pCp-derived photosensibilizers using the trifluoromethylated derivative **PS1** (Fig. 2). To our delight, the reaction of styrene **2a** in the presence of two equivalents of *n*-butane thiol **1a** in ethanol and 2.5 mol% of **PS1** under 405 nm LED irradiation afforded the corresponding thioether **3a** in 95% yield (entry 1). Importantly, catalyst loading could be reduced to 1 mol% with only a minor decrease in conversion (entry 2). Decreasing the quantity of thiol led to a significant decrease in the yield (entries 3 & 4), possibly due to the formation of disulfide *via* radical–radical coupling of thiyl radicals. Switching

from trifluoroacetophenone derived pCp to benzophenone derived pCp, with photosensitizers such as **PS2–4**, yielded **3a** in good yields (entries 5–7, 80–93%), demonstrating the potential in structural diversity of this family of photosensitizers. In contrast, **PS5**, a structurally analogous trifluoromethylketone lacking the pCp framework afforded **3a** in a lower yield (entry 8, 72%), underlining the importance of the through-space delocalization of the radical for the efficiency of the reaction. To better highlight the superior performance of **PS1**, classical ketones such **PS6** and **PS7** were evaluated and provided lower yields (entries 9 and 10, 53% and 45%, respectively). Control experiments confirmed that both light and photocatalyst are essential; in the absence of a photosensitizer, only 34% of **3a** was formed (entry 11), while the reaction in the dark yielded only trace amounts of product (entry 12).

The substrate scope of the reaction was then explored (Fig. 3). Using styrene as the olefin, a variety of thiols were evaluated. Primary aliphatic (**1a**), aromatic (**1b**) and benzylic (**1c**) thiols delivered the desired thioether products with good to excellent yields. However, the reaction is sensitive to the steric shielding of the thiol: the isolated yield decreases with a secondary thiol (**3d**, 55%), whereas a tertiary thiol afforded **3e** in only 15% NMR yield. Interestingly, functionalized thiols proved to be very efficient reaction partners, highlighting the chemoselectivity of this thiol–ene reaction. Notably, thiols bearing esters (**3f**, 78%), free amines (**3g**, 91%), amino acids (**3h**, 90%) and alcohols (**3i**, 80%) all provided the corresponding adducts efficiently, paving the way for potential late-stage functionalization.

The olefin partner was also broadly tolerated. An electron-deficient styrene derivative led to slightly decreased yield (**3j**, 70%) compared to its electron-rich analogue (**3k**, 91%). This trend is consistent with the electrophilic nature of the thiyl radical, for which addition on an electron-rich olefin is favored by polar effects. Heteroaromatic derivatives were also compatible, and **3l** was isolated in 97% yield. The reaction is again sensitive to steric considerations since 1-methylstyrene delivered the corresponding product **3m** with a moderate yield (41%). Alkyne substrates reacted efficiently, and product **3n** was isolated in 99% yield, with an $E : Z$ ratio of 85 : 15. Both terminal and cyclic non-activated olefins yielded the corresponding products with good yields (**3o**, 62% and **3p**, 77%, respectively). Additional functional groups were also tolerated on the olefin partner: allyl alcohol (**3q**, 84%) and vinyl acetate (**3r**, 82%) yielded the corresponding product in very good yield. In contrast, electron-poor olefins showed limited reactivity (**3s**, 37%), consistent with the inherent polarity mismatch (philicity) between an electrophilic thiyl radical and an electrophilic alkene acceptor.[20] This effect is further illustrated by the regioselective addition to 3-phenylacrylate, where exclusive addition at the α-ester-substituted position affords product **3t** in high yield. Finally, we investigated a photocatalytic radical cascade cyclization of *N*-tosyl diallyl amine, which accounts for a radical clock probe. The ring-closing product **3u** was obtained through a 5-*exo-trig* cyclisation, supporting the involvement of a radical mechanism.[21]
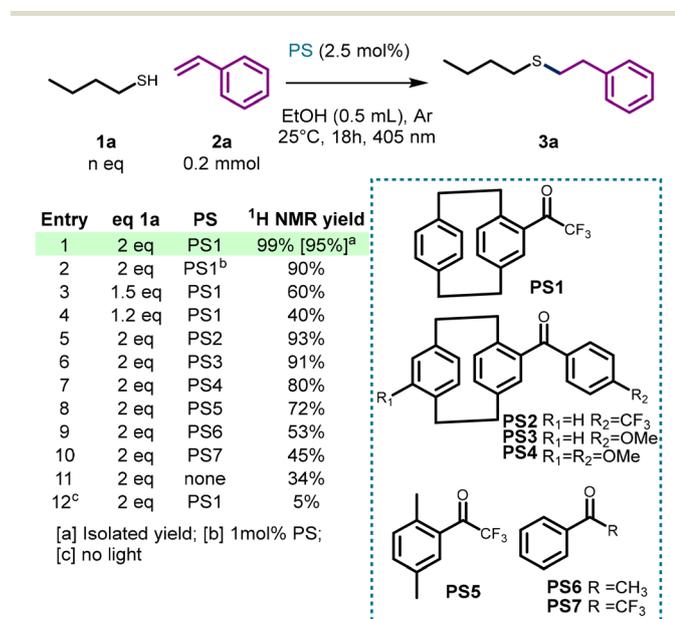

Entry	eq 1a	PS	^{1}H NMR yield
1	2 eq	PS1	99% [95%][a]
2	2 eq	PS1[b]	90%
3	1.5 eq	PS1	60%
4	1.2 eq	PS1	40%
5	2 eq	PS2	93%
6	2 eq	PS3	91%
7	2 eq	PS4	80%
8	2 eq	PS5	72%
9	2 eq	PS6	53%
10	2 eq	PS7	45%
11	2 eq	none	34%
12[c]	2 eq	PS1	5%

[a] Isolated yield; [b] 1mol% PS;
[c] no light

Fig. 2 Selected optimization of the photosensitizer and conditions, and control experiments.
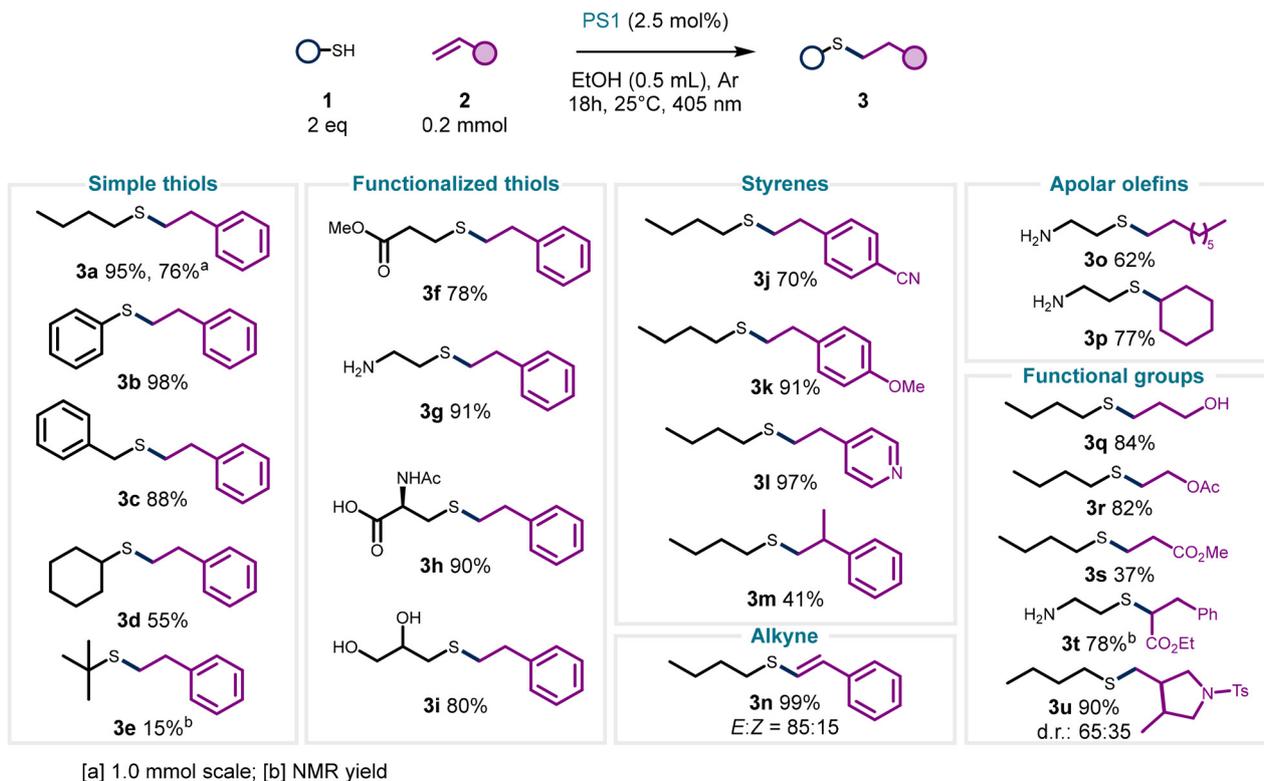
Fig. 3 Scope of the photochemical thiol–ene reaction (**1** (0.4 mmol), alkene (0.2 mmol), **PS1** (0.005 mmol) in EtOH (0.5 ml), and irradiation at 405 nm).

An important application of thiol–ene "click" chemistry, first emphasized by Hawker,[22] is its use as a key step in the synthesis of dendrimers.[23] In this regard, our metal-free methodology enabled the synthesis of the dendrimer precursor **3v** in an excellent 79% yield using only 2.5 mol% of **PS1** to form trifunctionalized **1v**, corresponding to only 0.8 mol% per addition (Fig. 4). The use of a cysteine derivative also provides

opportunities for post-functionalization and additional applications. This result highlights the potential of our approach for the synthesis of advanced molecular scaffolds under mild and green reaction conditions: the use of benign solvent (ethanol), low catalyst loading and ambient temperature.

Sunlight is the most renewable and unlimited source of energy. Developing photochemical transformation that only relies on sunlight as a source of energy is an important step towards sustainable chemistry. However, its relatively low intensity (*ca.* 2 mW cm^{-2}) explains why only a few applications have been reported.[6,24,25] Our system was found to be particularly efficient under sunlight activation[26] with only 6 h of sunlight irradiation on a sunny day of September (20–28 °C) in Marseille, France (Fig. 5). A range of substrates were tested in addition to the model substrate (**3a**, 75% ^{1}H NMR yield): vinylpyridine (**3l**, 72%), allyl alcohol (**3q**, 99%), thiophenol (**3b**, 99%) and benzylthiol (**3c**, 91%).

To complete our study, we evaluated the safety of **PS1** using a previously reported method in the presence of human liver cells (HepG2).[27] Cells were exposed for 48 h to different concentrations of **PS1**, and measurement of cell viability demonstrated the low toxicity of this photocatalyst with $CC_{50} >$ 200 μM (Fig. S20).

The recyclability of the catalyst further supports the sustainability of the system. Using 2.5 mol% of catalyst, recycling experiments performed over three consecutive runs delivered NMR yields of 85%, 72%, and 40%, corresponding to a cumu-
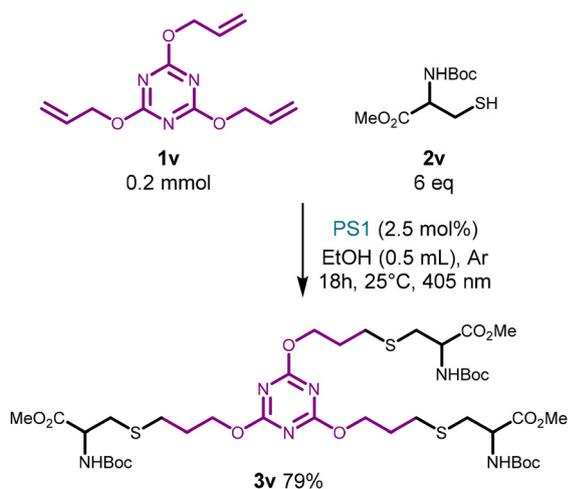

Fig. 4 Synthesis of the dendrimer precursor *via* photocatalytic thiol–ene reaction.
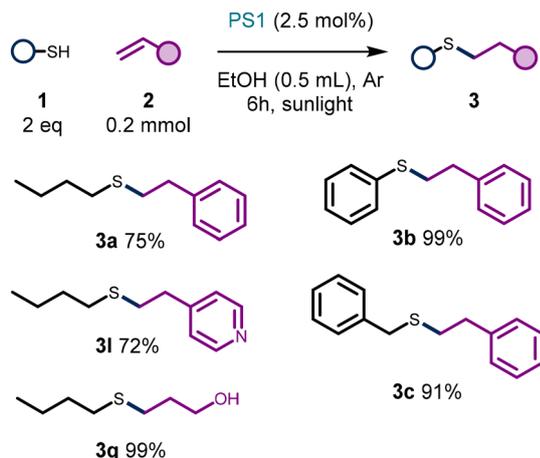
Fig. 5 Scope of the sunlight-irradiated thiol–ene reaction.

Fig. 6 Mechanistic experiments: (a) deuterium labelling experiments and (b) mechanism proposal.

lative turnover number (TON) of 80. These results demonstrate that the catalyst retains significant activity over multiple cycles, highlighting both its operational robustness and practical recyclability. A TON of 90 was achieved with a catalyst loading of 1% in a single reaction cycle (Fig. 2, entry 2).

To gain further insight into the reaction mechanism, we conducted a series of deuterium labelling experiments (Fig. 6a). First, the use of thiophenol-d_1 d-**1b** (89% of deuterium) afforded the corresponding product d-**4** with 74% deuterium incorporation at the benzylic position, indicating that the benzylic radical intermediate can abstract hydrogen (or deuterium) from the thiol substrate d-**1b** (chain propagation), or from the photosensitizer (photocatalytic mechanism). Additionally, irradiation of **PS1** in the presence of a large excess of d-**1b** resulted in the formation of the corresponding alcohol d-**5** bearing 40% deuterium at the α-OH position and no deuterium detected on the pCp bridge. This result rules out the possibility of intramolecular 1,5-HAT to generate a radical on the pCp bridge and confirms the formation of excited **PS1** diradical species. To evidence the implication of thiyl radicals in the mechanism, we then performed an EPR spin-trapping experiment in the presence of a DMPO trap. A solution of **PS1** (10 mM in t-Bu-benzene), n-BuSH (90 mM) and DMPO (100 mM) was irradiated at 405 nm for 30 seconds, an EPR signal was then registered on a Bruker EMX (Cavity 4103TM). As displayed in Fig. S19 (SI), the hyperfine coupling constants of $A_N = 1.33$ mT, $A_H = 1.08$ mT, $A_H = 0.1$ mT, and $A_H = 0.08$ mT were assigned to DMPO-butylthiyl radicals, confirming the radical character associated with the formation of thiyl radicals. In addition, when the spin trapping experiment was conducted under sunlight, the same signal with the same constants was recorded, confirming the formation of the thiyl radical initiating species as well (see the SI).

ON/OFF experiments using standard conditions showed that the reaction stops when subjected to darkness and starts again when irradiated (see details in the SI). However, a study from the Yoon group[28] revealed that termination events may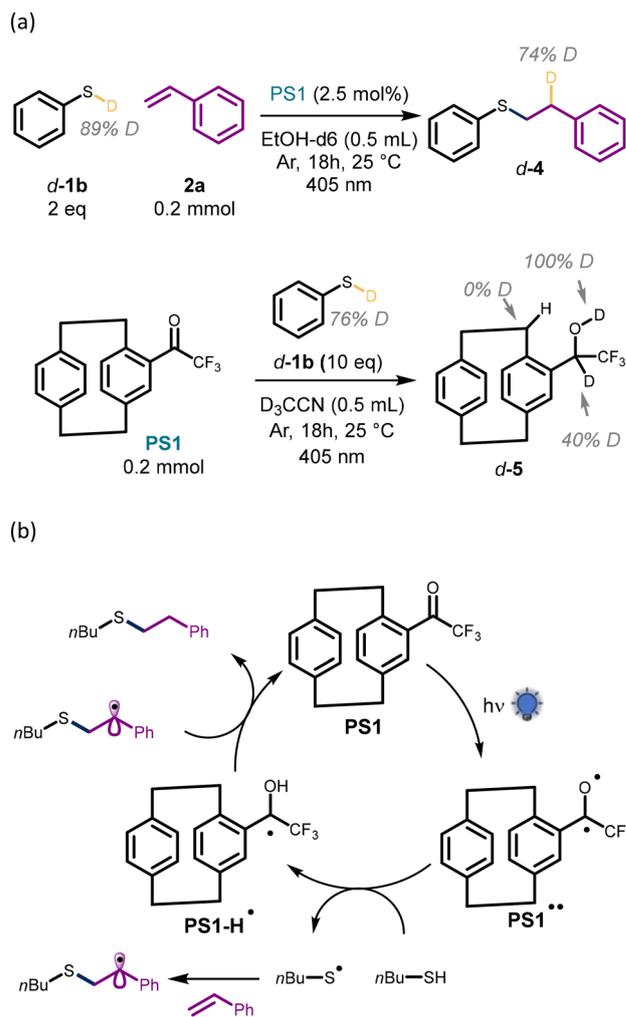 occur very rapidly (≪1 min), making it impossible to detect them through this type of experiment. We thus carried out quantum yield measurement experiment (see details in the SI).

The measured quantum yield (φ_{PS1}) for the thiol–ene reaction with **PS1** at 405 nm was 0.72 ($\varphi_{PS1} < 1$), suggesting a closed catalytic cycle – confirming the result of the ON/OFF experiment – and ruling out chain propagation mechanisms. A plausible mechanism for the formation of thioethers under the reaction conditions is proposed in Fig. 6. In the first step, **PS1** is irradiated and reaches its excited state. A hydrogen atom transfer (HAT) then occurs between the **PS1** diradical and n-butane thiol, leading to the formation of a thiyl radical.[29] This thiyl radical subsequently adds to the alkene, generating an alkyl radical. Finally, the alkyl radical abstracts a hydrogen atom from **PS1**-H, thereby regenerating **PS1** and affording the final thioether product. Fluorescence studies provided additional insight into the observed reactivity (see the SI for details). Stern–Volmer analysis revealed efficient quenching of the excited pCp catalyst by n-butane thiol, as demonstrated by the steep Stern–Volmer plot and the high quenching con-
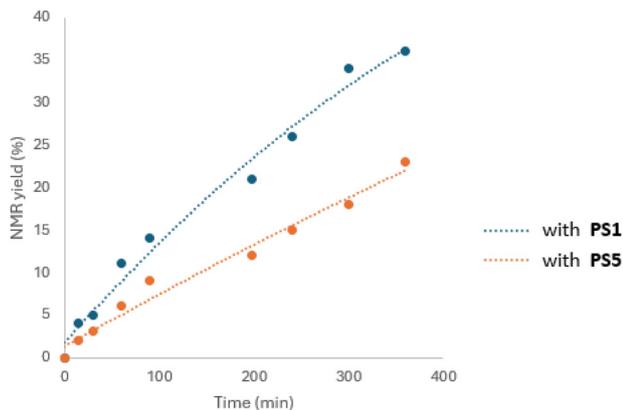
Fig. 7 Reaction kinetics monitored by NMR using CH_2Br_2 as an internal standard (**1a** (2.0 mmol), styrene (1.0 mmol), and **PS1** or **PS5** (0.025 mmol) in EtOH (2.5 ml)).

stant K_{SV} value (196.55 M^{-1}). This strongly supports a direct interaction between the excited state and the thiol, consistent with a productive photoinduced step (HAT), rather than simple physical deactivation. Additionally, the use of a disulfide reagent (Me$_2$S$_2$) in place of thiol did not allow any conversion, consistent with a mechanism involving HAT from thiol rather than energy transfer or redox (SET) mechanisms.

Besides the difference in isolated yields for **PS1** and **PS5** (Fig. 1), we also evaluated the quantum yield of the **PS5**-initiated reaction. Interestingly, this non-pCp photosensitizer displayed a quantum yield of $\varphi_{PS5} = 24$ ($\varphi_{PS5} \gg 1$, see details in the SI), indicating that the reaction proceeds predominantly through a chain propagation mechanism (smart initiation) rather than a truly photocatalytic cycle.[30] This result underscores the importance of through-space radical stabilization enabling the catalytic behavior of **PS1**.

We also compared the initial reaction kinetics of the two reactions, monitored by NMR. After 4 h, **PS1** achieved 26% conversion, whereas **PS5** reached only 15%, again demonstrating the superior performance of **PS1** and the crucial role played by the paracyclophane core in this transformation (Fig. 7).

In summary, we developed a green photochemical thiol–ene reaction compatible with natural sunlight irradiation. Importantly, the reaction proceeds with low catalytic loading of the photocatalyst and use of benign solvent under natural light with minimal energy input which further enhance the sustainability and environmental friendliness of the process. These photocatalysts exploit the through-space electronic delocalization of [2.2]-paracyclophane scaffolds which favors hydrogen atom transfer. Mechanistic studies – including deuteration experiments, EPR spin trapping, and quantum-yield determination – support a closed catalytic cycle involving HAT, ruling out a chain propagation pathway.

Conflicts of interest

There are no conflicts to declare.

Data availability

The bulk of the data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5gc06810j.

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