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Photoredox generation of isothiouronyl radical cations: a new platform in covalent radical catalysis.

Gaétan Archer⁺, Pierre Cavallère⁺, Maurice Médebielle, Jérémy Merad^{*}

Univ Lyon, Université Lyon 1, CNRS, INSA, CPE-Lyon, ICBMS

ICBMS, UMR 5246, Bat. Lederer

1 rue Victor Grignard, 69622 Villeurbanne (France)

E-mail: jeremy.merad@univ-lyon1.fr

[+] Equal contributions of these authors, alphabetical sorting

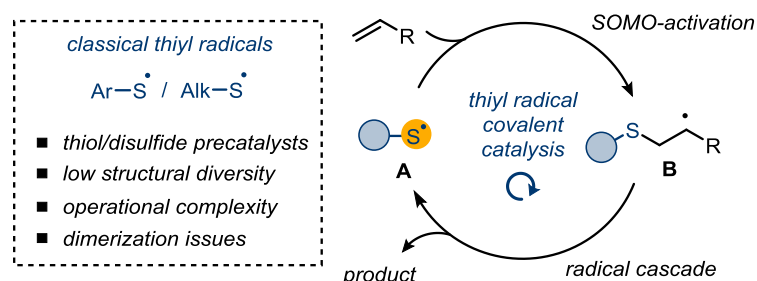
Abstract: Thiyl radicals offer unique catalytic patterns for the direct covalent activation of alkenes. However, important limitations in term of structural diversity and handling have hampered the routine use of thiyl radicals in covalent radical catalysis. Herein, we report a new class of cationic sulfur-centered radicals to achieve covalent radical catalysis. Their generation from highly modular thioureas by photoredox catalysis make their utilization very simple and reliable. The synthetic potential and the versatility of the catalytic system were finally evaluated in a (3+2)-radical cascade between vinylcyclopropanes and olefins.

Thiyl radicals are archetypal open-shell intermediates which have been extensively used for the synthesis of sulfur-containing molecules.^[1] In the field of catalysis, the unique properties of thiyl radicals - which are their relative stability, the ability to reversibly bind to C-C multiple bonds and the availability of simple thiol and disulfide precursors - have been responsible for the emergence of radical covalent organocatalysis.^[2] Indeed, the direct SOMO-activation of non-conjugated alkenes by the transient addition of catalytic thiyl radicals **A** and the formation of a carbon-centered radical **B** is an efficient strategy to trigger and control radical cascades (Scheme 1A). In 1988, a bright proof of concept was brought by Oshima^[3] and Feldman^[4] who independently reported the use of thiophenol thiyl radical catalyst to achieve *round trip* cascades between vinylcyclopropanes (VCP) and alkenes. However, the synthetic potential of using sulfur-centered radicals in covalent catalysis is counterbalanced by major practical issues. First, setting up soft conditions allowing the generation of thiyl radicals *in situ* from compliant precatalysts while preventing radical dimerization at a rate close to diffusion limit^[5] constitute longstanding challenges. More importantly, readily accessible thiyl radicals suffer a narrow structural diversity; therefore, they convey a uniform reactivity and offer limited options in optimizing original transformations. Partial solutions have been found in the slow addition of radical initiators and thiophenol precatalysts at high catalyst loadings,^[3,4,6] the tedious synthesis of hindered thiophenols,^[7] aerobic conditions and high temperatures,^[8] UV-irradiation of disulfides^[9] and visible-light irradiation of electron donor-acceptor (EDA) complexes,^[10] both of the two later narrowing the reaction scope. However, the persistent use of alkyl- and aryl-based thiyl radicals has perpetuated operational

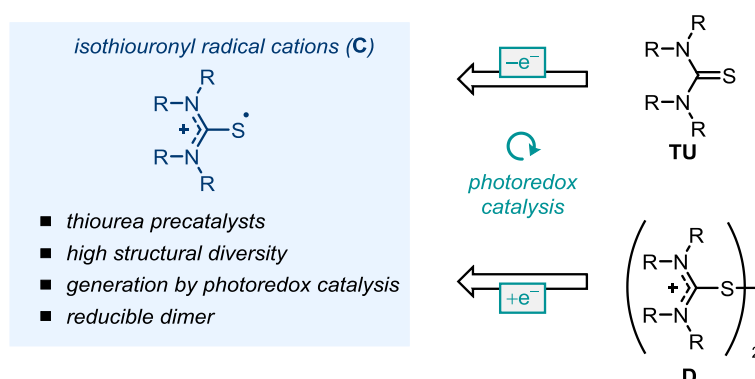
complexity and maintained covalent radical catalysis in its infancy for more than three decades. The development of a new class of thiyl radicals derived from readily available and modular precatalysts is then highly appealing to encourage the expansion of this promising field of research.^[11]

Thioureas constitute a broad family of easily accessible and modular sulfur-containing scaffolds. The presence of two mesomer-donor N-atoms makes thioureas strong S-Lewis bases and their oxidation by single electron transfer (SET) results in resonance stabilized isothiouronyl radical cations. Radicals generated from *N,N,N,N*-tetrasubstituted thioureas quickly evolve in stable and isolable dicationic disulfides.^[12] In 1981, Doyle and Blankespoor determined the oxidation potential of *N,N,N,N*-tetramethylthiourea ($E_{ox} \leq +0.95$ V vs Ag/Ag⁺ in acetonitrile) and the resulting dicationic dimer was shown to undergo reduction at -0.51 V (vs Ag/Ag⁺).^[13] Based on these precedents, we hypothesized that *N,N,N,N*-tetrasubstituted thioureas (**TU**) could provide highly modular platforms to access sulfur-centered radicals **C** (Scheme 1B). We envisioned that the generation of the sulfur-centered radical, either via oxidation of **TU** or reduction of the dicationic dimer **D**, could be ensured by an appropriate photoredox catalyst through very mild and operationally simple conditions.

A. General scheme of thiyl-based radical covalent catalysis:



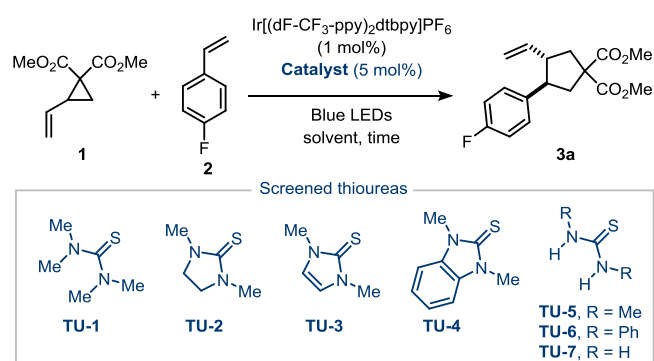
B. Isothiouronyl radical cations from thioureas (this work):



Scheme 1. A. General scheme of thiyl radical covalent catalysis from classical thiyl radicals; B. Photoredox/tetrasubstituted thiourea dual catalysis (our strategy).

We first aimed to reach a proof of concept by testing the commercially available *N,N,N,N*-tetramethylthiourea (**TU-1**) as a potential precatalyst in a model (3+2) cycloaddition between VCP **1** and 4-fluorostyrene **2**. The reported redox potentials of **TU-1** and the corresponding disulfide have guided the choice of Ir[(dF-CF₃-ppy)₂dtbpy]PF₆ (Ir(III)^{*}/Ir(II) = +1.21 V; Ir(III)/Ir(II) = -1.37 V vs SCE in CH₃CN) as a photoredox cocatalyst. After irradiating the mixture with blue LEDs for 17 h, cyclopentane **3a** was obtained in a 65% yield then confirming our working hypothesis (Table 1, entry 1). For comparisons, thiophenol (entry 2) and thiophenolate (entry 3) displayed low efficiency as thiyl radical precursors, highlighting the power of thioureas as precatalysts. The influence of the catalyst scaffold on the reaction efficiency was investigated by synthesizing (one or two steps) and screening different precatalysts derived from imidazoline (TU-2), imidazole (TU-3) and benzimidazole (TU-4). The substitution pattern of the thiourea has a dramatic impact on the catalytic activity (entries 4 to 6) and then constitutes an essential parameter in reaction optimization. In this case, TU-4 turned out to be the best precatalyst, probably due to extended aromaticity. The fused phenyl ring also prevents undesirable side reactions between TU-4 and nucleophiles or radicals. The substitution degree was also identified as an important element since *N,N,N,N*-disubstituted (TU-5, TU-6) and non-substituted (TU-7) thioureas delivered **3a** in low yields (entries 7 to 9). The number of N-substituents does not correlate with the measured redox potentials of thioureas (see SI) and cannot explain these results. It is more likely that the collapse of the unstable radical cations and/or disulfides reduces drastically the catalyst turn over number.^[14] Further optimization revealed that switching the solvent (solvent screening in the SI) for MeOH delivers **3a** in a quantitative yield (entry 10). With this setup, fully organocatalytic conditions (4-CzIPN as organophotocatalyst) can be applied although with slightly decreased yields (entry 11). Finally, increasing the amount of **2** (2 equiv.) allowed the reaction to proceed efficiently in 4 hours (entry 12). It is noteworthy that the reaction diastereoselectivity remained unchanged regardless the reaction settings, with a 80:20 (trans:cis) ratio under the best conditions (entry 12).

Table 1.
reaction



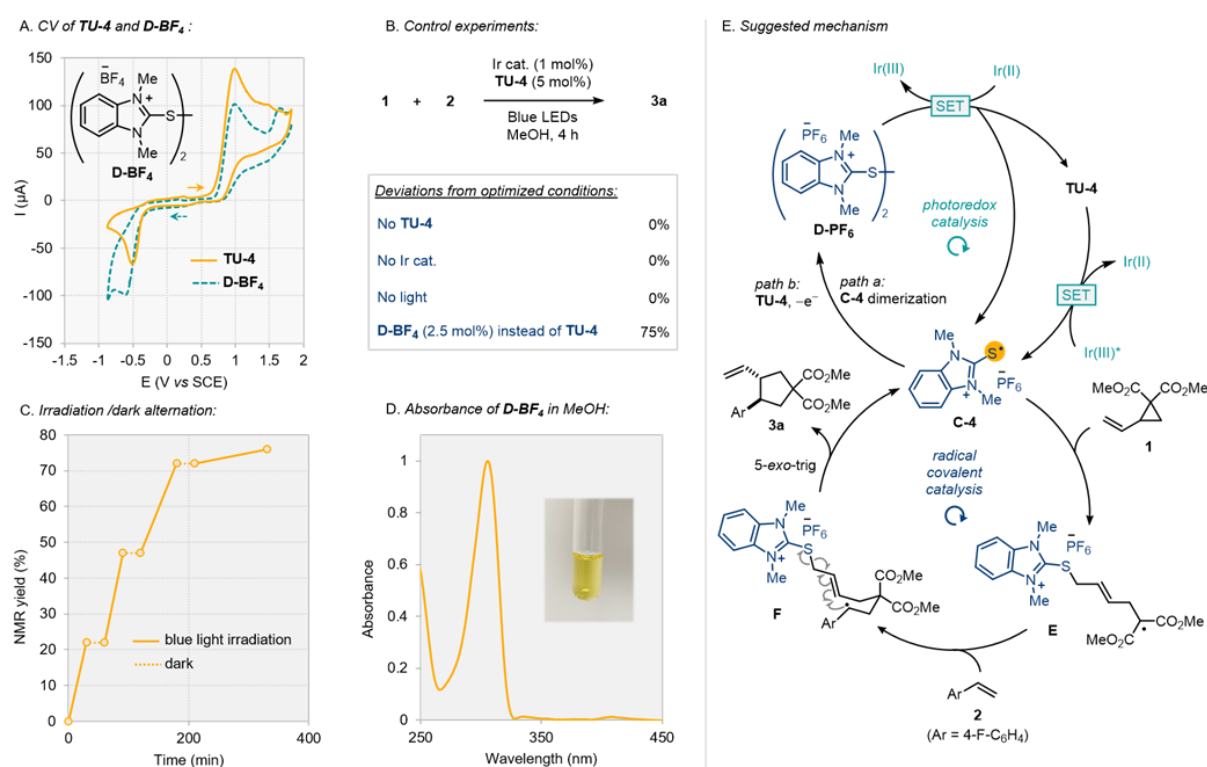
Optimisation of the conditions.^[a]

entry	catalyst	Equiv. of 2	solvent	yield of 3 ^[b] (%) ^[c]
1	TU-1	1	CH ₃ CN	65%
2	PhSH	1	CH ₃ CN	0%
3 ^[d]	PhSH	1	CH ₃ CN	19%
4	TU-2	1	CH ₃ CN	8%
5	TU-3	1	CH ₃ CN	44%
6	TU-4	1	CH ₃ CN	90%
7	TU-5	1	CH ₃ CN	10%
8	TU-6	1	CH ₃ CN	34%
9	TU-7	1	CH ₃ CN	0%
10	TU-4	1	MeOH	99% (76%)
11 ^[e]	TU-4	1	MeOH	81%
12 ^[f]	TU-4	2	MeOH	98% (87%)

[a] Initial conditions: 1 (0.2 mmol), 2 (0.2 mmol), Ir cat (1 mol%), TU-4 (1 mol%), solvent (1.0 mL), irradiation with blue LEDs (40 W Kessil®) under argon atmosphere, 17 h; [b] Determined by ¹⁹F NMR analysis of the crude reaction mixture using PhOCF₃ as internal standard; [c] isolated yield; [d] K₂CO₃ (1.0 equiv.) [e] 4-CzIPN (1 mol%) instead of Ir cat.; [f] 4 hours instead of 17 hours.

We next performed mechanistic investigations aiming to unravel the entanglement of the two catalytic cycles. Cyclic voltammetry (CV) measurements revealed that TU-4 displayed an irreversible oxidation step at +0.98 V (in MeOH vs SCE) (Scheme 2A, orange curve) with the immediate formation of the dicationic dimer characterized with a reduction at -0.51 V.^[13] This assumption was validated by synthesizing the dimer D-BF₄ whose reduction potential was measured at -0.61 V (Scheme 2A, green curve). Then, each molecule can reversibly be formed from the other by opposite electron transfer events. It is noteworthy that the dimer formation can occur following two concomitant but hard to distinguish pathways: a) the radical homo-coupling; b) the radical addition onto the unreacted thiourea followed by a second single-electron oxidation of the radical cation adduct.^[12a, 14] Control experiments revealed that the two catalysts and light are mandatory for the reaction to proceed (Scheme 2B). The photoredox catalyzed reduction of dicationic complex also leads to isothiouronyl radical cation since 3a was obtained in a 75% yield when D-BF₄ (2.5 mol%) was used as precatalyst (Scheme 2B). A last set of experiments was done to clarify the role of the Ir complex which could catalyse SET during the whole reaction or only act as a radical initiator. Alternating blue light irradiation and dark sequences indicated that the radical cascade was interrupted every time the light was turned off (Scheme 2C). It means that the thiyl radical reaches out an inactive resting-state (TU-4 or D-PF6) in the absence of light. Neither TU-4 or the yellow dication D ($\lambda_{\text{max}} = 308$ nm in MeOH, Figure 2D) can be converted in isothiouronyl radical by direct photolysis with blue light (450 nm). Therefore, the recovery of the catalytic

activity when turning on the light again can only be explained by SET from the photoredox catalyst. These observations rule out the chain process and confirm a fully photocatalyzed process. (Scheme 2D). Based on these findings, a plausible mechanism is depicted in scheme 2E. First, the single-electron oxidation of TU-4 provides the thiyl radical C-4 which is quickly trapped by VCP 1 leading to E. The subsequent ring opening/radical addition sequence results in the formation of intermediate F. The ultimate 5-exo-trig cyclization releases radical C-4 and 3a in a favoured trans configuration. Note that the dr remains constant during the whole process (see SI) providing evidence that no equilibration of the relative configuration (by hydrogen atom transfers at the allylic or benzylic positions) occurs. In a last step, the dicationic dimer D-PF₆, would be reduced by Ir(II) in C-4 and TU-4.^[15]



Scheme 2. A. Cyclic voltammetry of TU-4 (orange curve, -> oxidation) and D-BF₄ (green curve, -> reduction), MeOH/NBu₄PF₆ [0.1 M], glassy carbon (3 mm), $\nu = 0.2$ V/s; B. Control experiments, yields determined by ¹⁹F NMR using PhOCF₃ as internal standard; C. Time-dependent formation of 3 through irradiation/dark alternation, monitored by ¹⁹F NMR using PhOCF₃ as internal standard; D. Optical absorbance spectrum of D-BF₄; E. Plausible reaction mechanism.

After having demonstrated that N,N,N,N-tetrasubstituted thioureas act as suitable thiyl radical precursors, we envisioned to explore the synthetic potential of our catalytic system. First, the model reaction was scaled-up to 2.0 mmol scale providing 3a in satisfying yields even with 1 mol% of TU-4 and 0.2 mol% of the photoredox catalyst (Figure 1A). The functional group tolerance was then investigated by varying the olefin partner. Styrene derivatives remain suitable substrates independently from the substitution pattern (3b, 3c) and α -methyl styrene has proved to be an excellent reaction partner (3d). 1,3-Dienes also

provide the corresponding vinyl cyclopentanes in good yields without any traces of 7-membered ring formation (3e, 3f). Non activated alkenes can efficiently participate in the radical cascade (3g) and spiro compounds derived from methylene cyclopentane and β -pinene have been isolated in 90% (3h) and 86% (3i), respectively. Enamines (3j, 3k) vinyl ethers (3l) and vinylsulfide (3m) can be used to introduce amide, ether and thioether groups. Interestingly, the cycloaddition can be performed in the presence of vinylboronic esters in moderate yields leading to elaborate boronic esters 3n and 3o. Those compounds and amides derivatives 3j and 3k display the higher levels of diastereoselectivity probably due to an increased steric demand. Internal olefins constitute valuable entries to fused bicyclic structures (3p) even if the less favourable steric environment impacts the reaction efficiency. The transformation was then conducted onto polyfunctional natural products or analogues revealing that electron rich (3r) and poor (3s) trisubstituted alkenes, carboxylic acids (3t), carbonyls (3u), enamide and polyols (3v) are perfectly tolerated. Replacing methyl esters on the VCP by ethyl esters (4a), nitriles (4b), carboxylic acid (4c) or halogen atoms (4d, 4e) does not affect the transformation efficiency (Figure 1B).[16] The moderate yields obtained using commercially available dihalogenated VCPs are due to the use of 1 equivalent of alkene 2 and the difficult purification of highly these apolar compounds. Gem-difluoro cyclopentanes are interesting bioisosteres of tetrahydrofurans and no straightforward catalytic access have been reported so far. The structural diversity was improved by using disubstituted VCPs resulting in 1,3,4-trifunctionalized cyclopentanes (4f, 4g). The crossing of various VCPs and olefins is compatible with the binary catalytic system providing the N- and F-containing molecule 4h and the spiro/spiro tricyclic compound 4i. The reaction limitations are inherent to the reactivity of substrates and radical intermediates and not to the catalytic system itself (Figure 1C). The use of dodecene afforded 3w in a low yield probably due to the highly reversible addition of poorly reactive olefin to the radical intermediate E (Scheme 2E). Electron poor alkenes constitute refractory substrates since their addition to E is kinetically and thermodynamically disfavoured (3x). Spiro-VCPs are also unreactive substrates in this transformation (4j). In the meantime, the reported catalytic system has proved to be competitive with previous approaches relying on hydrazonyl[17] and bromyl radicals[18] since proceeding with short reaction times and with high functional group tolerance.

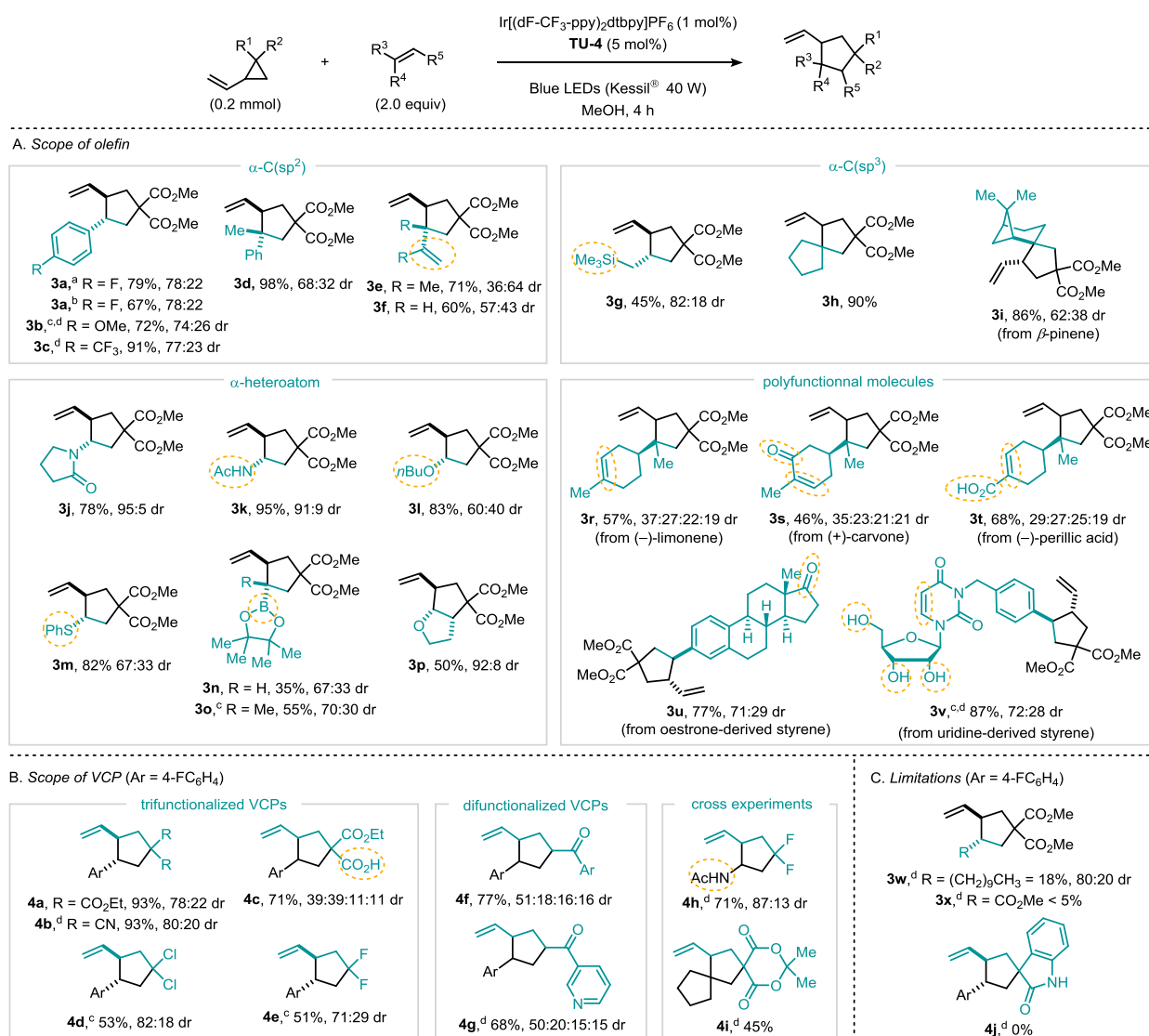


Figure 1. Reaction scope. [a] reaction performed on 2.0 mmol; [b] Ir cat (0.2 mol%), TU-4 (1 mol%); [c] 1 equivalent of olefin, [d] Reaction performed on 17 h.

In conclusion, we have reported the first use of isothiouronyl radical cations to achieve covalent catalysis. The photoredox-catalyzed generation of the sulfur-centered radical from thioureas offers mild and user-friendly conditions while providing a high functional group tolerance. We expect that the highly modular platform offered by thioureas would motivate new developments in the discrete field of radical covalent catalysis. Notably, the setup of enantioselective cascades remains a central challenge due to the difficulty to access chiral thiyl radicals. Chiral thioureas are readily synthesized by sulfuration of chiral azolium salts (N-heterocyclic carbene precursors) and offer tremendous opportunities to investigate asymmetric transformations. We are currently pursuing these efforts in this direction.

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Keywords: covalent catalysis • photocatalysis • radical ions • thioureas • thiyl radicals

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