

Radical Chemistry

A Photochemical Organocatalytic Strategy for the α -Alkylation of Ketones by using RadicalsDavide Spinnato⁺, Bertrand Schweitzer-Chaput⁺, Giulio Goti, Maksim Ošeka, and Paolo Melchiorre*

In memory of Dieter Enders (1946–2019)

Abstract: Reported herein is a visible-light-mediated radical approach to the α -alkylation of ketones. This method exploits the ability of a nucleophilic organocatalyst to generate radicals upon S_N2 -based activation of alkyl halides and blue light irradiation. The resulting open-shell intermediates are then intercepted by weakly nucleophilic silyl enol ethers, which would be unable to directly attack the alkyl halides through a traditional two-electron path. The mild reaction conditions allowed functionalization of the α position of ketones with functional groups that are not compatible with classical anionic strategies. In addition, the redox-neutral nature of this process makes it compatible with a cinchona-based primary amine catalyst, which was used to develop a rare example of enantioselective organocatalytic radical α -alkylation of ketones.

Introduction

The α -alkylation of ketones is a fundamental C–C bond-forming process.^[1] Classically, it is accomplished by means of highly nucleophilic alkali metal enolates, generated by deprotonation of the corresponding ketones, which can react with alkyl halides through an S_N2 pathway (Figure 1 a).^[2] This two-electron, anionic strategy has found extensive use in synthesis. However, it also brings about some chemoselectivity issues because the strongly basic and nucleophilic nature of the metal enolates limits the range of functional groups that

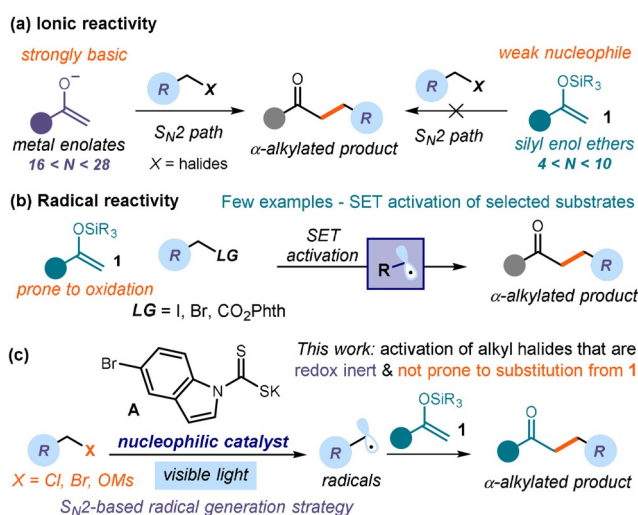


Figure 1. (a) Traditional strategies for the α -alkylation of ketones by using enolate equivalents via anionic pathways. (b) Radical approach to the alkylation of silyl enol ethers **1**. (c) The presented photochemical strategy uses a nucleophilic catalyst **A** and visible light to generate radicals from redox-inert alkyl electrophiles, which are then trapped by weakly nucleophilic silyl enol ethers.

can be tolerated. Milder alternatives, which avoid the use of strongly basic metal enolates, are therefore highly sought-after. Silyl enol ethers are stable enolate equivalents that are easy to synthesize and to handle.^[3] These compounds have been extensively used in nucleophilic addition chemistry (aldol, Michael, and Mannich-type processes).^[4] However, the poor nucleophilicity^[5] of silyl enol ethers makes them unsuitable for alkylation reactions with alkyl halides via an S_N2 pathway (Figure 1 a, right arrow). The literature contains only a few reports of silyl enol ether alkylation, generally limited to S_N1 -type substitution processes.^[6]

In principle, the high reactivity of open-shell intermediates, which can easily engage in C–C bond-forming processes,^[7] could be used for effective reactions with the weakly nucleophilic silyl enol ethers **1** (Figure 1 b). Moving from a two-electron logic to a radical reactivity pattern could therefore provide the desired degree of chemoselectivity and functional-group tolerance to the α -alkylation of ketones. However, effective strategies to generate alkyl halide-derived radicals would be required. To date, the few reported protocols are limited to the use of specific radical precursors that can be easily activated by initiators or through single-electron-transfer (SET) processes, including perfluoroalkyl

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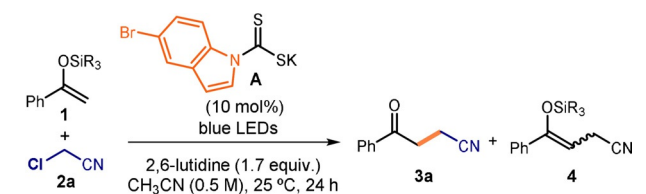
iodides,^[8] α -bromo ketones and esters,^[9] and *N*-(acyloxy)-phthalimide derivatives.^[10] In addition, redox-based strategies (e.g. photoredox catalysis)^[11] offer an additional challenge because the low oxidation potentials of silyl enol ethers^[12] make them prone to degradation upon SET oxidation.

Our laboratory recently reported a unique photochemical catalytic radical generation strategy that is not reliant on the redox properties of the substrates.^[13] This method exploits the ability of a highly nucleophilic^[14] dithiocarbonyl anion organocatalyst **A** to generate radicals upon blue light irradiation and S_N2 -based activation of substrates (including alkyl chlorides and mesylates) that would be inert to classical radical-generating strategies (Figure 1c). Herein, we demonstrate how this catalytic platform can provide a general radical approach for the α -alkylation of ketones by using silyl enol ethers. This approach synthetically complements and enriches traditional two-electron strategies. This is because the mild reaction conditions and functional-group tolerance allowed us to functionalize the α position of ketones with moieties that are incompatible with classical anionic processes.

Results and Discussion

We commenced our studies by evaluating the alkylation of acetophenone-derived silyl enol ether **1**, using the commercially available chloroacetonitrile **2a** as the radical precursor (Table 1). The experiments were conducted at 25 °C in acetonitrile, with a blue LED strip emitting at 465 nm,

Table 1: Optimization studies and control experiments.^[a]



Entry	Deviation from standard conditions	SiR ₃	1	Yield 3/4 [%] ^[b]
1	none	TMS	a	71 / 5
2	none	TBS	b	7 / 93
3	none	TIPS	c	<5 / >95
4	H ₂ O (20 equiv)	TBS	b	90 / 8
5	work up: TFA or TBAF	TBS	b	91 ^[c] / 0
6	work up: CH ₃ SO ₃ H or HCl _(aq)	TBS	b	>95 / 0
7	no light	TBS	b	0
8	no catalyst A	TBS	b	0
9	TEMPO (1 equiv)	TBS	b	0
10	<i>fac</i> -Ir(ppy) ₃ (1 mol%); no catalyst A	TBS	b	5 / 40

[a] Reactions performed on a 0.2 mmol scale at 25 °C for 24 h using 0.4 mL of CH₃CN under illumination by blue LED strip ($\lambda_{\text{max}} = 465$ nm, 14 W) and using catalyst **A** (10 mol%), 1.5 equiv of **1a**, and 1.7 equiv of lutidine. [b] Yield and distribution of products **3** and **4** determined by ¹H NMR analysis of the crude mixture using trichloroethylene as the internal standard. [c] Yield of isolated **3a**. TMS: trimethylsilyl, TBS: *tert*-butyldimethylsilyl, TIPS: triisopropylsilyl, TFA: trifluoroacetic acid, TBAF: tetrabutyl ammonium fluoride.

10 mol% of the dithiocarbonyl anion catalyst **A**, adorned with an indole chromophoric unit, and a slight excess of **1** (1.5 equiv). When using the trimethylsilyl derivative **1a**, these conditions furnished the desired ketone product **3a** in good yield along with traces of the silyl derivative **4** (entry 1). The use of different silyl protecting groups, including *tert*-butyldimethylsilyl (TBS) and triisopropylsilyl (TIPS), provided better chemical yields and selectively favored the formation of the O-silylated adduct **4** (entries 2 and 3, respectively). Considering the cost of the silyl enol ethers and the efficiency of the reaction, we continued our investigations with the TBS derivative **1b**. Adding water to the reaction mixture allowed us to directly achieve ketone **3a** as the major product (entry 4). However, this hydrolysis step was not uniformly effective for all of the silyl enol ethers evaluated, therefore, we treated the crude mixture with trifluoroacetic acid or tetrabutylammonium fluoride (TBAF), which quantitatively and consistently led to complete conversion of **4** into the target product **3a** (entry 5). Effective hydrolysis can be also achieved in the presence of acids; methanesulfonic acid or HCl in H₂O (4 equiv, entry 6) afforded **3a** in high yields.

Control experiments confirmed that the alkylation reaction could not proceed in the absence of light or catalyst **A** (entries 7 and 8). The presence of a radical scavenger (TEMPO, 1 equiv) completely suppressed the reaction (entry 9), whereas traces of the cyanomethyl-TEMPO adduct could be detected. Importantly, our attempts to perform the model reaction by using classical enolate chemistry, for example, treating acetophenone with strong bases, met with failure (see Table S2 in the Supporting Information). Finally, we demonstrated that the strongly reducing *fac*-Ir(ppy)₃ photoredox catalyst provided vastly inferior results (entry 10), presumably because of a difficult generation of the reactive radical from **2a**.

Using the optimized conditions described in Table 1, entry 5, we tested the generality of the photochemical organocatalytic α -alkylation process (Figure 2). Firstly, we evaluated the scope of the carbon radicals that could be intercepted by the silyl enol ether **1b**. A large variety of electrophilic primary radicals afforded the corresponding α -alkylated ketones in good yields (**3a**, **3e**, **3h**). Secondary radicals could also be generated and efficiently intercepted by **1b**, albeit, in some cases, there was a need to perform the reaction at 60 °C (adducts **3b-d**, **3f-g**). Benzylic radical precursors, bearing both electron-rich and electron-poor aryl substituents, were also competent substrates (products **3i-n**). The strategy can be used to implement a radical α -amino-methylation process, allowing the introduction of a protected primary amine (**3o**) along with a trifluoromethyl moiety (**3p**). The reaction could be performed on a gram scale without the loss of efficiency (7.0 mmol scale, **3a** obtained in 91 % yield, 1.0 g).

We then evaluated the compatibility with unprotected polar functional groups, which is an important criterion for assessing the potential applicability of a method to the synthesis of complex molecules and drug discovery.^[15] Our approach displayed a good level of tolerance towards heterocycles containing nitrogen, sulfur, and oxygen atoms (**3q-s**).

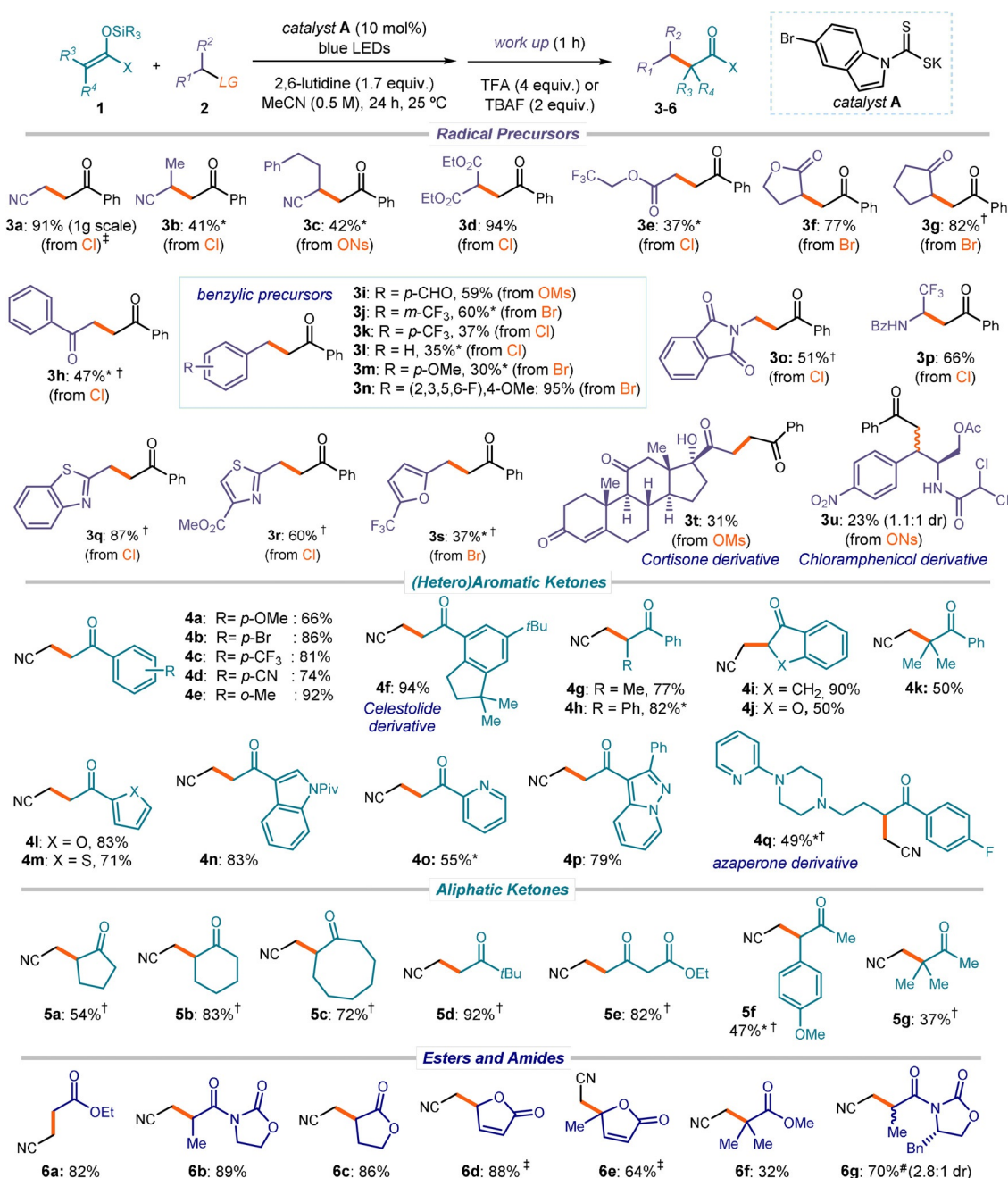


Figure 2. Reaction scope: reactions performed on 0.5 mmol scale by using 1.5 equiv of **1** and 1.0 mL of acetonitrile; yields of products refer to isolated material after purification; the bold orange bond denotes the newly formed C–C bond. *Performed at 60 °C. [†]Using dichloroethane as the solvent. [‡]Reaction time: 48 hours, [#]3.0 equiv of silyl enolate. TFA: trifluoroacetic acid, TBAF: tetrabutylammonium fluoride, Piv: *tert*-butylacyl, Ms: mesyl, Ns: nosyl.

In addition, good tolerance was achieved for functional groups that would be incompatible with classical anionic alkylation strategies or Lewis acid activation, including unprotected alcohols (**3f**), amide N–H bonds (**3p**), esters (**3e** and **3r**), ketones (**3g** and **3h**), enones (**3t**), and aldehydes (**3i**). Finally, cortisone (**3t**) and chloramphenicol (**3u**) derivatives could be used as radical precursors, highlighting the potential of this method for the synthesis of complex molecules. As a limitation of the system, alkyl bromides leading to non-stabilized primary and secondary radicals and

to tertiary radicals could not be activated. A list of moderately successful and unsuccessful substrates for this radical alkylation strategy is reported in Figure S4 of the Supporting Information.

We then demonstrated that silyl enol ethers derived from aromatic ketones could intercept the electrophilic radical generated from chloroacetonitrile **2a**. A variety of substitution patterns on the aryl ring, with different electronic (**4a–e**) or steric profiles (**4e**, **4f**), could be easily accommodated. Importantly, easily oxidizable heterocyclic substrates (**4l–m**)

or nitrogen-containing heterocycles (**4n–p**) are readily tolerated. A substrate derived from azaperone, containing an aminopyridine and a piperazine moiety, could be alkylated in moderate yield (**4q**). Cyclic and acyclic silyl enol ethers could also be used in this radical alkylation process, leading to the corresponding aliphatic ketones (**5a–5g**). Interestingly, selective alkylation at the terminal position of a β -ketoester was achieved (**5e**), exploiting the modularity of silyl enolate synthesis compared to classical alkali metal enolates. Finally, O,O and N,O silyl ketene acetals were also suitable substrates and afforded the corresponding α -alkylated esters and amides in high yields (**6a–6g**). A chiral oxazolidinone could be used to give moderate diastereoselectivity (**6g**). This strategy also provides a tool for forging quaternary carbon centers by using different silyl enolates (**4k**, **5g**, and **6e–f**).

A benefit of this protocol is that it can rely on radical precursors **2** bearing different leaving groups, including halides (Cl or Br) and sulfonates (OMs or ONs). The choice of the leaving group can therefore be dictated by its ease of access or compatibility with other functional groups in a complex synthetic plan.

To showcase the synthetic utility of the system, we used this strategy for the stereoselective catalytic α -functionalization of ketones (Figure 3). Although effective catalytic enantioselective methods are available, they are limited to ionic chemistry.^[16] The direct asymmetric α -alkylation of ketones with radicals remains a difficult target.^[17] This is in contrast to the radical functionalization of aldehydes, for which the combination of enamine-mediated catalysis and photoredox catalysis recently provided useful tools for the

design of asymmetric processes.^[18] The lack of application in the enamine-mediated functionalization of ketones is due to the peculiar structure of the *cinchona*-based primary amine **B**.^[19] This chiral amine is often the catalyst of choice in ionic chemistry because it can trap different electrophiles with consistently high stereocontrol upon activation of ketones by enamine formation. However, catalyst **B** bears an easily oxidizable tertiary amine moiety, which makes it incompatible with a photoredox catalyst usually needed to generate the reactive open-shell intermediate. In principle, the redox-neutral nature of our radical-generation strategy means that catalysts **A** and **B** could coexist. As depicted in Figure 3, this possibility was translated into experimental reality to develop an enantioselective direct radical α -alkylation of cyclic ketones **7**. The dithiocarbamate anion catalyst **A** effectively activated chloride **2a** toward radical formation, and the hydroquinidine-derived amine **B** secured the formation of a chiral enamine upon condensation with **7**, which could easily trap the radical. This photochemical strategy afforded the corresponding α -cyanoalkylation products **8a–h**.^[20] Although cyclohexanone derivatives provided high stereocontrol (**8a–g**), a five-membered ring proved less reactive and stereoselective (**8h**). Interestingly, acid-sensitive functionalities, including an acetal or a Boc group, were tolerated well (**8e** and **8f**). This asymmetric alkylation could be extended to other alkyl chloride radical precursors; 2,4-dinitrobenzyl chloride and phenacyl chloride afforded the corresponding alkylated products (**8i** and **8j**) with good results.

The proposed catalytic cycle of the photochemical radical alkylation of silyl enol ethers is outlined in Figure 4. The nucleophilic catalyst **A** attacks^[14] the alkyl halide **2** to form the photon-absorbing intermediate **I**.^[21] Blue light irradiation triggers the cleavage of the weak C–S bond to generate a pair of radicals **II** and **III**.^[22] The silyl enol ether **1** is reactive enough to intercept the carbon-centered radical **II**, leading to the α -oxo-stabilized radical **IV**. SET between **IV** and the sulfur-centered radical **III** regenerates catalyst **A** and forms the oxocarbenium ion **V**, which can easily hydrolyze to afford the final α -alkylated ketone **3**.^[23] To glean insights into the mechanism, we measured the quantum yield (Φ) of the model reaction, which was found to be as low as 0.05 ($\lambda = 460$ nm, using potassium ferrioxalate as the actinometer, experiments performed both with a stoichiometric amount of intermediate **I** and under catalytic conditions, see Section E.5 in the Supporting Information for details). This result suggests that a radical-chain process, based on either a dithiocarbamate-group-transfer mechanism or a SET from radical **IV** to intermediate **I**, is highly unlikely (see Section E.6 for these alternative mechanistic pathways).

Mechanistically, we also evaluated the possibility for the dimeric adduct **VI**, arising from the self-reaction of the sulfur-centered radical **III**, to be generated during the process (Figure 4). We did indeed detect intermediate **VI** under catalytic conditions. In addition, an authentic sample of **VI** (5 mol%) catalyzed the model reaction when irradiated with blue LEDs, affording product **3a** in quantitative yield (no reaction was observed in the dark). These observations suggest that dimer **VI** is a photoactive species in equilibrium with the progenitor radical **III**. This dimerization pathway

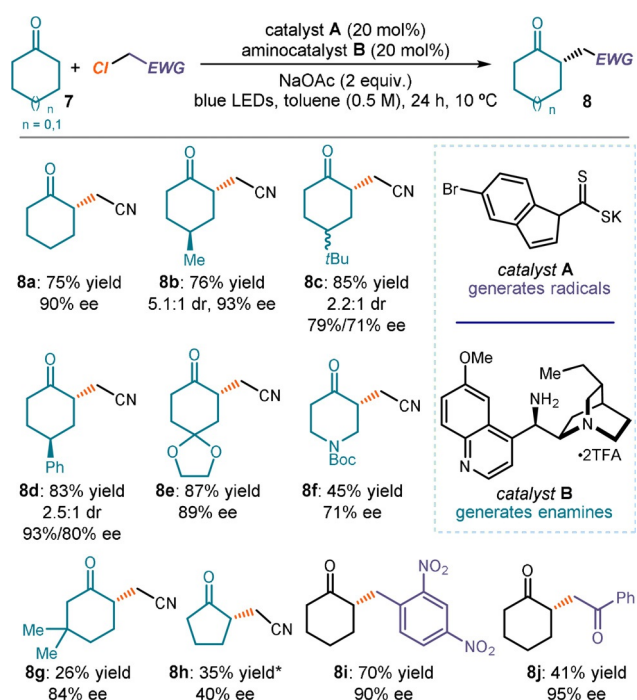


Figure 3. Aminocatalytic enantioselective photochemical α -alkylation of cyclic ketones with alkyl chloride derived radicals. Reactions performed on a 0.2 mmol scale; yields refer to isolated material. The reactivity was completely inhibited in the absence of light. *Reaction performed at 25 °C.

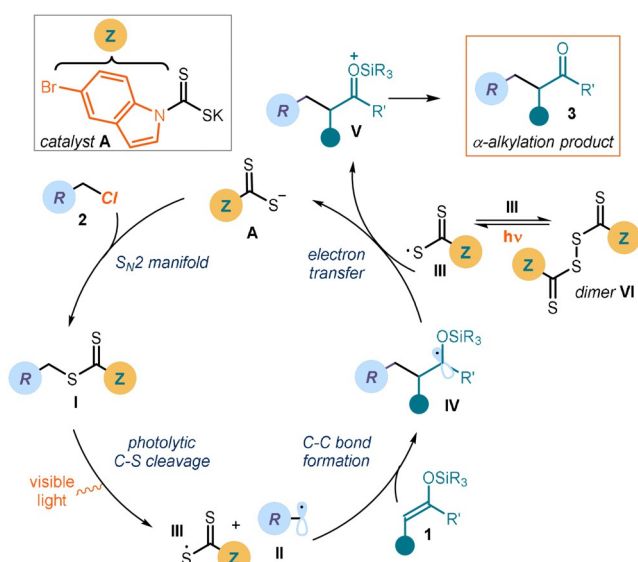


Figure 4. Proposed catalytic mechanism for the visible-light-driven radical alkylation of silyl enol ethers; Z: chromophore.

confers a longer lifetime to **III**,^[24] facilitating the turnover of catalyst **A** (SET reduction from **IV**).

Conclusion

In summary, we have developed a visible-light-mediated organocatalytic strategy for the radical α -alkylation of ketones by using silyl enol ethers. This process synthetically complements traditional two-electron strategies. The mild reaction conditions and functional-group tolerance allowed us to install, at the α position of the ketone, moieties not compatible with classical anionic processes. In addition, the redox-neutral conditions of this process make it tolerant of a *cinchona*-based amine catalyst, which was used to develop an enantioselective variant.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enamines · photochemistry · radical chemistry · silyl enolates · α -alkylation

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- [22] With the aim to evaluate its direct implication within the mechanistic path, we synthesized the adduct of type **I** by reacting equimolar amounts of the dithiocarbonyl anion **A** and chloroacetonitrile **2a**. 10 mol% of this type **I** intermediate could effectively promote the model reaction (**3a** formed in 95% yield). In addition, light irradiation of adduct **I** in the presence of TEMPO led to the formation of the cyanomethyl–TEMPO adduct in 60% yield (see Section E4 in the Supporting Information for details).
- [23] Cross-coupling of the α -oxo radical **IV** and the sulfur-centered radical **III**, cannot be excluded. This process would provide the exact same product of the SET pathway proposed in Figure 4 because the ensuing adduct would collapse to afford oxocarbenium ion **V** and catalyst **A**. This alternative mechanistic pathway is detailed in Figure S21 of the Supporting information.
- [24] This dimerization behavior could infer a persistent radical character to intermediate **III**, see: a) D. Leifert, A. Studer, *Angew. Chem. Int. Ed.* **2020**, *59*, 74–108; *Angew. Chem.* **2020**, *132*, 74–110; b) K. S. Focsaneanu, J. C. Scaiano, *Helv. Chim. Acta* **2006**, *89*, 2473–2482.

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