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A Photochemical Organocatalytic Strategy for the α-Alkylation of Ketones using Radicals**

*Davide Spinnato,[‡] Bertrand Schweitzer-Chaput,[‡] Giulio Goti, Maksim Ošeka, and Paolo Melchiorre**

In memory of Professor Dieter Enders

***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 method's mild reaction conditions allowed us to functionalize 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 via deprotonation of the corresponding ketones, which can react with alkyl halides through a S_N2 manifold (Figure 1a).[2] This two-electron, anionic strategy has found extensive use in synthesis. However, it also brings about some chemoselectivity issues, since the strongly basic and nucleophilic nature of the metal enolates limits the range of functional groups that 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, which are easy to synthesize and to handle.[3] They have been extensively used in nucleophilic addition chemistry (aldol, Michael, and Mannich-type processes).[4] However, their poor nucleophilicity[5] makes them unsuitable for alkylation reactions with alkyl halides via a S_N2 manifold (Figure 1a, 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 1b). 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, this would require effective strategies to generate alkyl halide-derived radicals. 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 perfluoralkyl 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 since 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, which 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), which would be inert to classical radical-generating strategies (Figure 1c). Here, we demonstrate how this catalytic platform can provide a general radical approach for the α-alkylation of ketones using silyl enol ethers. This approach synthetically complements and enriches traditional two-electron strategies. This is because the method's 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.

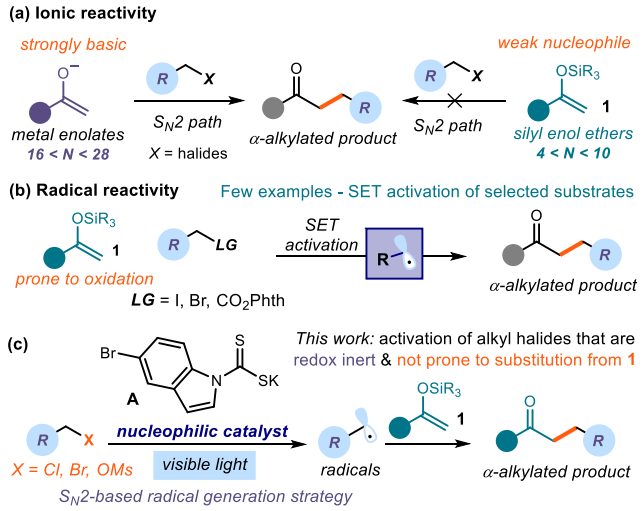

Figure 1. (a) Traditional strategies for the α-alkylation of ketones using enolate equivalents via anionic pathways. (b) Radical approach to the alkylation of silyl enol ethers **1**. (c) The presented photochemical strategy uses a nucleophilic catalyst **A** and visible light to generate radicals from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

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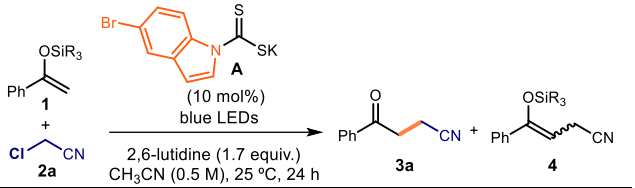
Results and Discussion

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, using a blue LED strip emitting at 465 nm, 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 while selectively favoring 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, since this hydrolysis step was not uniformly effective for all the silyl enol ethers evaluated, 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, since methanesulfonic acid or HCl in H_2O (4 equiv., entry 6) afforded **3a** in high yields.

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



entry	*deviation*	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_2O (20 equiv.)	TBS	**b**	90 / 8
5	*Work up:* TFA or TBAF	TBS	**b**	91[c] / 0
6	*Work up:* CH_3SO_3H 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	*fac*-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 CH_3CN under illumination by blue LED strip (λ_{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 ^{1}H NMR analysis of the crude mixture using trichloroethylene as the internal standard. [c] Yield of isolated **3a**. [d] After work up with TFA. TMS: trimethylsilyl, TBS: *tert*-butyldimethylsilyl, TIPS: triisopropylsilyl, TFA: trifluoroacetic acid, TBAF: tetrabutyl ammonium fluoride.

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 using classical enolate chemistry, *e.g.* 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). We first 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 heating 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-aminomethylation 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 losing 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 a method's potential applicability to complex molecule synthesis and drug discovery.[15] Our approach displayed a good level of tolerance towards heterocycles containing nitrogen, sulfur, and oxygen atoms (**3q-s**). 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 (**3t**), 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 complex molecule synthesis. As a limitation of the system, alkyl bromides leading to non-stabilised 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 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.

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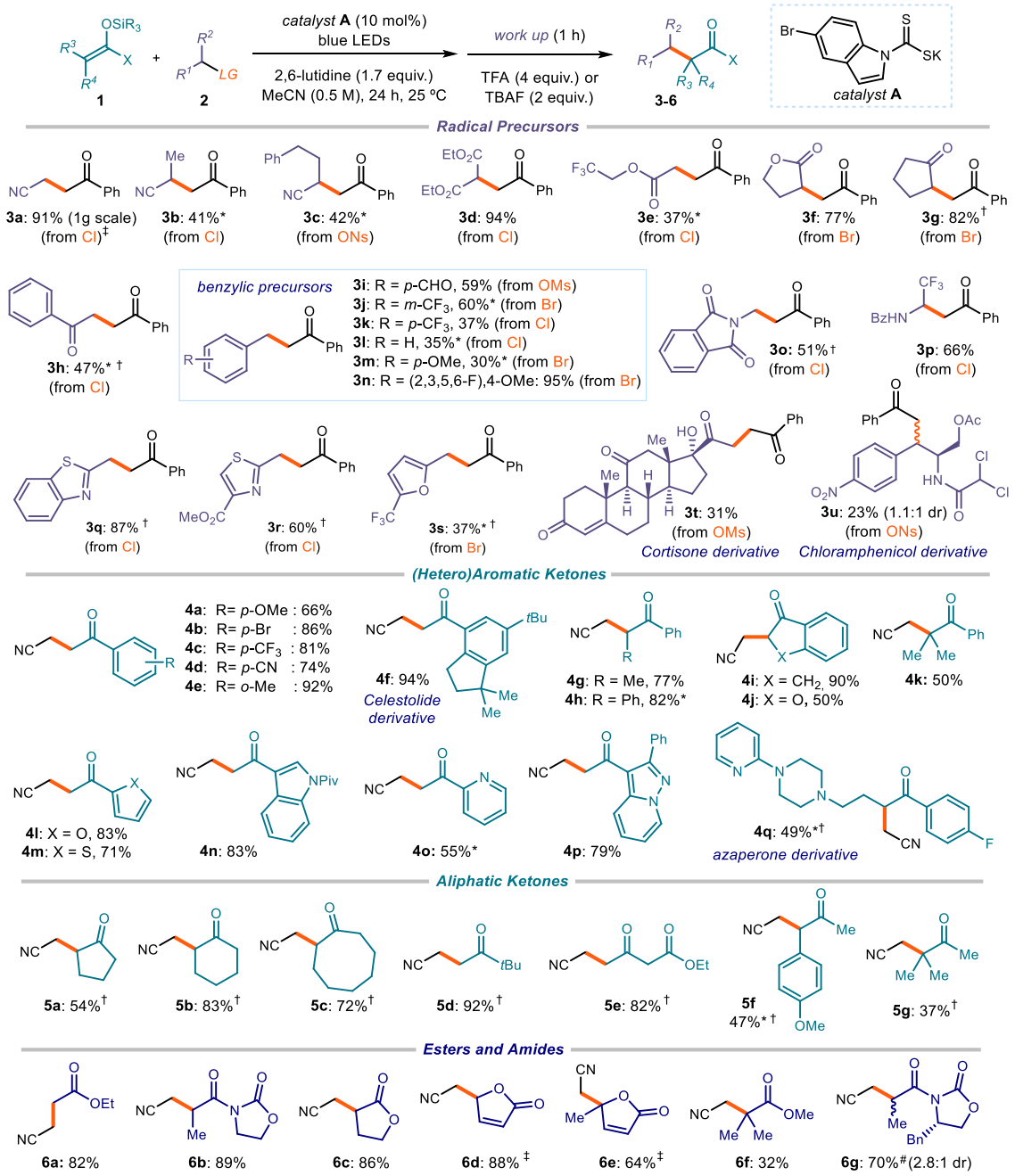

Figure 2. Reaction scope: reactions performed on 0.5 mmol scale using 1.5 equiv. of **1** and 1.0 mL of acetonitrile; yields of products refer to isolated material after purification; the bold orange bond denotes the newly formed C-C bond. * Performed at 60 °C. † Using dichloroethane as the solvent.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

To showcase the system's synthetic utility, we used this strategy for the stereoselective catalytic α-functionalization of ketones (Figure 3). While 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, where the combination of enamine-mediated catalysis and photoredox catalysis recently provided useful tools for designing asymmetric processes.[18] The lack of application in the enamine-mediated functionalization of ketones is ascribable 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 via enamine formation. However, catalyst **B** bears an easily oxidazable 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 4, 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, while 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] While 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, since 2,4-dinitrobenzyl chloride and phenacyl chloride afforded the corresponding alkylated products (**8i** and **8j**) with good results.

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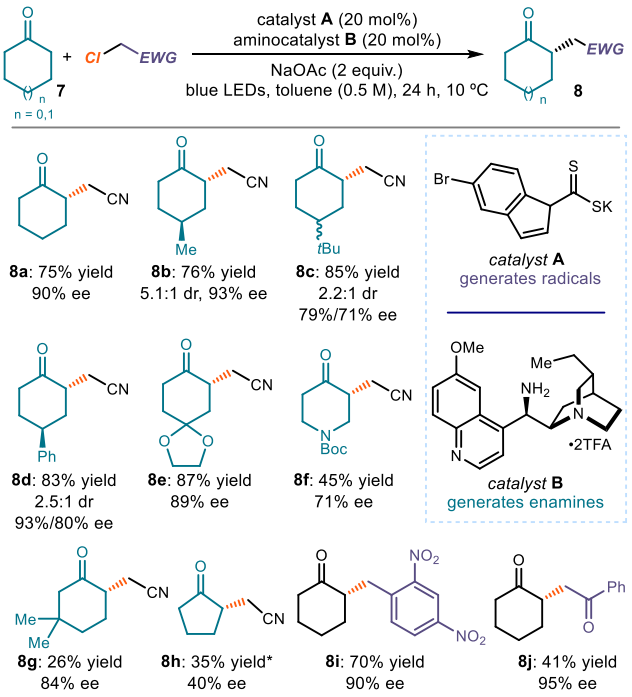

Figure 3. Aminocatalytic enantioselective photochemical α-alkylation of cyclic ketones with alkyl chloride-derived radicals. Reactions performed on a 0.2 mmol scale; yields refer to isolated material. The reactivity was completely inhibited in the absence of light. *Reaction performed at 25 °C.

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-alkylation 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 (λ = 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 manifold 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 indeed detected 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 manifold confers a longer lifetime to **III**,[24] facilitating the turnover of catalyst **A** (SET reduction from **IV**).

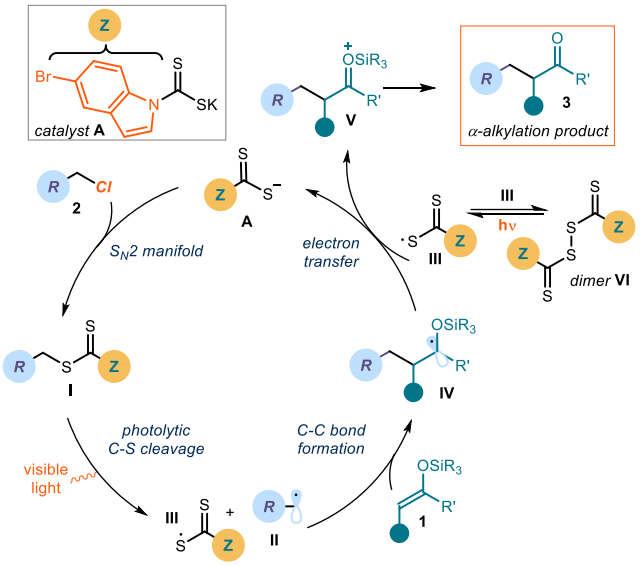

Figure 4. Proposed catalytic mechanism for the visible-light-driven radical alkylation of silyl enol ethers; Z: chromophore.

Conclusion

In summary, we have developed a visible-light-mediated organocatalytic strategy for the radical α-alkylation of ketones using silyl enol ethers, which synthetically complements traditional two-electron strategies. The method's mild reaction conditions and functional group tolerance allowed us to install, at the ketones' α position, 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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[1] a) R. E. Ireland, *Organic Synthesis*, Prentice-Hall, Englewood Cliffs, 1969; b) E. M. Carreira, L. Kvaerno, α-Functionalization of Enolates, *Classics in Stereoselective Synthesis*, Wiley-VCH, Weinheim, 2007, chapter 3, pp 69–102.

[2] a) F. A. Carey, R. J. Sundberg, Alkylation of Enolates and Other Carbon Nucleophiles, in *Advanced Organic Chemistry Part B: Reactions and Synthesis*, Springer, New York, 2007, 5th Ed, pp 1–62; b) D. Stolz, U. Kazmaier, Metal Enolates as Synthons in Organic Chemistry In *PATAI'S Chemistry of Functional Groups*; Z. Rappoport, Ed. 2010. For Selected examples of α-alkylation of ketones with quaternary ammonium enolates, see: c) I. Kuwajima, E. Nakamura, *J. Am. Chem. Soc.* **1975**, *97*, 3257–3258; d) I. Kuwajima, E. Nakamura, *Acc. Chem. Res.* **1985**, *18*, 181–187.

[3] a) G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc.* **1968**, *90*, 4462−4464; b) J. K. Rasmussen, *Synthesis* **1977**, 91−110.

[4] a) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509; b) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, *2*, 1011−1014. For reviews, see: c) J. Matsuo, M. Murakami, *Angew. Chem. Int. Ed*. **2013**, *52*, 9109–9118; *Angew. Chem.* **2013**, *125*, 9280–9289; d) S. B. J. Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108; *Angew. Chem.* **2013**, *125*, 9267 – 9279. Selected examples of Mukaiyama-Michael addition reactions: e) K. Narasaka, K. Soai, T. Mukaiyama, *Chem. Lett.* **1974**, 1223−1224; f) D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142.

For reviews on Mannich-type reactions: g) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.* **1998**, *37*, 1044−1070; *Angew. Chem.* **1998**, *110*, 1096-1122; h) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069−1094.

[5] a) A. I. Leonov, D. S. Timofeeva, A. R. Ofial, H. Mayr, *Synthesis* **2019**, 1157−1170. For a freely accessible database of nucleophilicity parameters *N* of silyl enolates, see: http://www.cup.lmu.de/oc/mayr/DBintro.html.

[6] For a review of reactions of alkyl chlorides with silyl enolates via S_N1 pathways, see a) M. T. Reetz, *Angew. Chem. Int. Ed.* **1982**, *21*, 96–108; *Angew. Chem.* **1982**, *94*, 97-109. For selected examples: b) M. T. Reetz, W. F. Maier, *Angew. Chem. Int. Ed.* **1978**, *17*, 48–49; *Angew. Chem.* **1978**, *90*, 50; c) Y. Nishimoto, M. Yasuda, A. Baba, *Org. Lett.* **2007**, *9*, 4931–4934; d) Y. Nishimoto, T. Saito, M. Yasuda, A. Baba, T*etrahedron* **2009**, *65*, 5462–5471.

[7] a) *Radicals in Organic Synthesis*, P. Renaud, M. P. Sibi (Eds), Wiley-VCH: Weinheim, Germany, 2001. b) *Encyclopedia of Radicals in Chemistry, Biology and Materials*, C. Chatgilialoglu, A. Studer (Eds); John Wiley & Sons, 2012. (c) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714.

[8] Selected examples: a) K. Miura, M. Taniguchi, K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 6391–6394; b) K. Mikami, Y. Tomita, Y. Ichikawa, K. Amikura, Y. Itoh, *Org. Lett.* **2006**, *8*, 4671–4673; c) P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2011**, *50*, 6119−6122; *Angew. Chem.* **2011**, *123*, 6243–6246.

[9] Selected examples: a) E. Baciocchi, E. Muraglia, *Tetrahedron Lett.* **1994**, *35*, 2763−2766; b) D. P. Curran, S.-B. Ko, *Tetrahedron Lett.* **1998**, *39*, 6629–6632; c) E. Arceo, E. Montroni, P. Melchiorre, *Angew. Chem. Int. Ed.* **2014**, *53*, 12064−12068; *Angew. Chem.* **2014**, *126*, 12260–12264; d) N. Esumi, K. Suzuki, Y. Nishimoto, M. Yasuda, *Org. Lett.* **2016**, *18*, 5704−5707.

[10] The following protocols are effective for a wide scope of alkyl electrophiles, since unstabilized primary radicals as well as secondary and tertiary alkyl radicals can be successfully used. However, they are limited to acetophenone-derived silyl enol ethers: a) W. Kong, C. Yu, H. An, Q. Song, *Org. Lett.* **2018**, *20*, 349−352; b) M.-C. Fu, R. Shang, B. Zhao, B. Wang, Y. Fu, *Science* **2019**, *363*, 1429–1434.

[11] M. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926.

[12] S. Fukuzumi, M. Fujita, J. Otera, Y. Fujita, *J. Am. Chem. Soc.* **1992**, *114*, 10271–10278.

[13] a) B. Schweitzer-Chaput, M. A. Horwitz, E. de Pedro Beato, P. Melchiorre, *Nat. Chem.* **2019**, *11*, 129–135; b) S. Cuadros, M. A. Horwitz, B. Schweitzer-Chaput, P. Melchiorre, *Chem. Sci.* **2019**, *10*, 5484–5488; c) D. Mazzarella, G. Magagnano, B. Schweitzer-Chaput, P. Melchiorre, *ACS Catal.* **2019**, *9*, 5876−5880.

[14] For a study discussing the high nucleophilicity of dithiocarbonate and dithiocarbamate anions of type **A**, see: X.-H. Duan, B. Maji, H. Mayr, *Org. Biomol. Chem.* **2011**, *9*, 8046–8050.

[15] a) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, *10*, 383–394; b) W. R. Pitt, D. M. Parry, B. G. Perry, C. R. Groom, *J. Med. Chem.* **2009**, *52*, 2952–2963.

[16] a) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329; b) R. Cano, A. Zakarian, G. P. McGlacken, *Angew. Chem. Int. Ed.* **2017**, *56*, 9278–9290; *Angew. Chem.* **2017**, *129*, 9406 –9418.

[17] For the few catalytic examples reported so far, see: a) A. Mastracchio, A. A. Warkentin, A. M. Walji, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U.S.A.*, 2010, **107**, 20648–20651; b) E. Arceo, A. Bahamonde, G. Bergonzini, P. Melchiorre, *Chem. Sci.* **2014**, *5*, 2438–2442; c) Y. Zhu, L. Zhang, S. Luo, *J. Am. Chem. Soc.* **2014**, *136*, 14642–14645.

[18] a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80. For a review: b) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41–49.

[19] P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770**;** *Angew. Chem.* **2012**, *124*, 9886–9909.

[20] For an example of asymmetric catalytic α-cyanoalkylation of aldehydes using easily reducible bromoacetonitrile as the radical precursor, see: E. R. Welin, A. A. Warkentin, J. C. Conrad, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2015**, *54*, 9668−9672; *Angew.Chem.* **2015**, *127*, 9804–9808.

[21] Substrates bearing thio functions, including xanthates, have been extensively used in stoichiometric amounts to generate radicals, see: a) D. H. R. Barton, S. Z. Zard, *Pure Appl. Chem.* **1986**, *58*, 675–684; b) S. Z. Zard, *Angew. Chem. Int. Ed.* **1997**, *36*, 672–685; *Angew Chem.* **1997**, *109*, 724-737. For strategies based on xanthate derivatives to synthesize ketones, see: c) M. R. Heinrich, S. Z. Zard, *Org. Lett.* **2004**, *6*, 4969-4972; d) S. Z. Zard, *Acc. Chem. Res.* **2018**, *51*, 1722−1733; d) S. Z. Zard, *Helv. Chim. Acta* **2019**, *102*, e1900134.

[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 manifold proposed in Figure 4, since 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.* DOI: 10.1002/anie.201903726; b) K. S. Focsaneanu, J. C. Scaiano, *Helv. Chim. Acta.* **2006**, *89*, 2473–2482.

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Radical Chemistry

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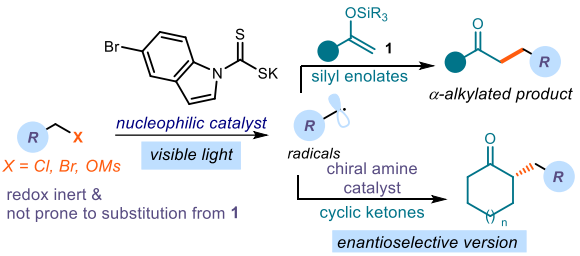
A Photochemical Organocatalytic Strategy for the α-Alkylation of Ketones using Radicals



Radical time to alkylate ketones. We report a visible-light-mediated radical approach that enables the α-alkylation of ketones using alkyl electrophiles recalcitrant to traditional ionic pathways. The redox-neutral nature of this process makes it compatible with a chiral amine catalyst, which was used to develop a rare example of enantioselective organocatalytic α-alkylation of cyclic ketones via a radical path.