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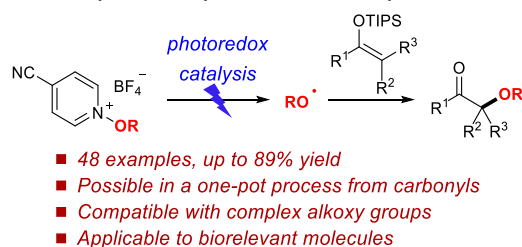
Intermolecular C–O Bond Formation with Alkoxy Radicals: Photoredox-Catalyzed α -Alkoxylation of Carbonyl Compounds.

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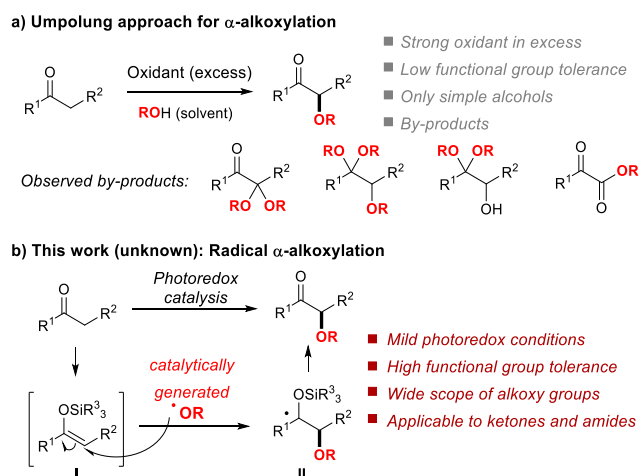
Radical α -alkoxylation of silyl enol ethers and silylketene N,O-acetals



ABSTRACT: Due to the high reactivity of alkoxy ($\text{RO}\cdot$) radicals and their propensity to easily undergo β -scission or Hydrogen Atom Transfer (HAT) reactions, intermolecular alkoxylation involving $\text{RO}\cdot$ radicals are barely described. We report herein for the first time the efficient intermolecular trapping of alkoxy radicals by silyl enol ethers. This photoredox-mediated protocol enables the introduction of both structurally simple and more complex alkoxy groups into a wide range of ketones and amides.

Alkoxy radicals ($\text{RO}\cdot$) are key intermediates implied in many natural processes, ranging from atmospheric chemistry to biology.¹ Due to their high reactivity, they hold a special place in the field of radical chemistry, quite different from their alkyl analogs. Notably, their development as a reactive species in organic chemistry is mainly limited to their high propensity to undergo HAT or β -scission reactions.² These reactivities usually lead to the generation of a more stable C-centered radical, which is then engaged in C–C or C–Heteroatom bond formation. A third reactivity of $\text{RO}\cdot$ radicals consists in their ability to directly add onto alkenes, thus involving the formation of a C–O bond.³ However, these alkoxylation reactions are mostly performed in an intramolecular fashion, in order to be competitive with fast HAT/ β -scission pathways.^{4–5} Conversely, the development of alkoxylation reactions involving a highly challenging intermolecular $\text{RO}\cdot$ addition onto alkenes or other unsaturated systems is still at its infancy.⁶ In this article we report the first intermolecular addition of alkoxy radicals to silyl enol ethers. This methodology leads to the synthesis α -alkoxylated carbonyls, which are versatile synthetic compounds used in many fields of application.⁷ In spite of this wide interest, the C–H alkoxylation in α position to carbonyl compounds has only been scarcely studied so far although its development would be an important added-value over existing methods. Indeed, as no “ RO^+ ” electrophile is readily available,⁸ a classical strategy which would involve the

Scheme 1. Strategies for C–H α -alkoxylation of carbonyl compounds.



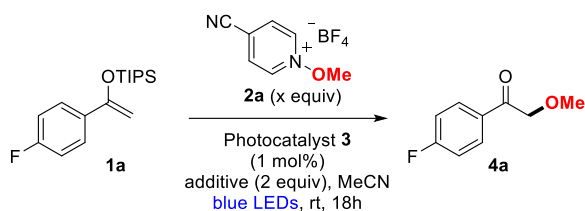
activation of the carbonyl substrate into a nucleophilic intermediate (enolate, silyl enol ether, enamine...) is unadapted. To date, only “umpolung” approaches have been developed: the ketone substrate is oxidized and further reacts with a nucleophilic alcohol ROH (Scheme 1a).⁹ Such umpolung strategy has however two major drawbacks: i) excess amounts of strong oxidants ($m\text{CPBA}$, $\text{Pb}(\text{OAc})_4$, $\text{PhI}(\text{OAc})_2$, *tert*-butyl peroxide...) are required, which leads

to poor functional-group compatibility and/or to substantial amounts of by-products; ii) the corresponding alcohol is always used as solvent or co-solvent, which limits the application scope to structurally simple alkoxy groups (mostly OMe and OEt).

Our new radical-based α -alkoxylation strategy overcomes these issues. Indeed, given the recent successful developments using photoredox catalysis,² our approach is based on the mild photocatalytic generation of RO \cdot radicals, and involves only stoichiometric amounts of the precursor of both structurally simple and more complex alkoxy moieties. For the success of our methodology, we hypothesized that silyl enol ethers **I**, easily generated from the corresponding carbonyl compounds, would be suitable substrates to efficiently trap RO \cdot radicals in an intermolecular manner (Scheme 1b). The resulting α -silyloxy C-centered radical **II** would be highly stabilized and other HAT/ β -scission pathways would then be minimized.

Within this framework, we started our study by examining the alkoxylation of silyl enol ether **1a** in presence of Ir(ppy)₃ **3a** as the photocatalyst (1 mol%, Table 1). Based on our previous work, *N*-methoxypyridinium salt **2a** was

Table 1. Optimization of the photoredox-catalyzed α -methoxylation of silylated enol ether **1a.^a**



Entry	Photocatalyst	x	Additive	Yield (%) ^b
1	Ir(ppy) ₃ 3a	1.2	-	27
2	3a	1.2	Na ₂ CO ₃	58
3	3a	1.2	KOAc	17
4	3a	1.2	Na ₂ HPO ₄	<5
5	3a	1.2	K ₂ HPO ₄	61
6	3a	1.2	K ₃ PO ₄	45
7	3a	1.2	Et ₃ N	-
8	3a	1.2	pyridine	15
9	3a	1.2	2,6-lutidine	50
10	3a	1.5	K ₂ HPO ₄	75
11	3a	1.8	K ₂ HPO ₄	78
12	Eosin Y 3b	1.8	K ₂ HPO ₄	35
13	Rose Bengal 3c	1.8	K ₂ HPO ₄	40
14	Ru(bpy) ₃ (PF ₆) ₂ 3d	1.8	K ₂ HPO ₄	90 (89) ^c
15	-	1.8	K ₂ HPO ₄	-
16 ^d	3d	1.8	K ₂ HPO ₄	-

^aGeneral conditions: **1a** (0.2 mmol), **2a** (x equiv), **3** (1 mol%) and additive (2 equiv) in 2 mL of MeCN irradiated with blue LEDs at rt for 18 h. ^bYields determined by ¹⁹F NMR spectroscopy using fluorobenzene as an internal standard. ^cYield into brackets refers to chromatographically pure product. ^dIn the dark.

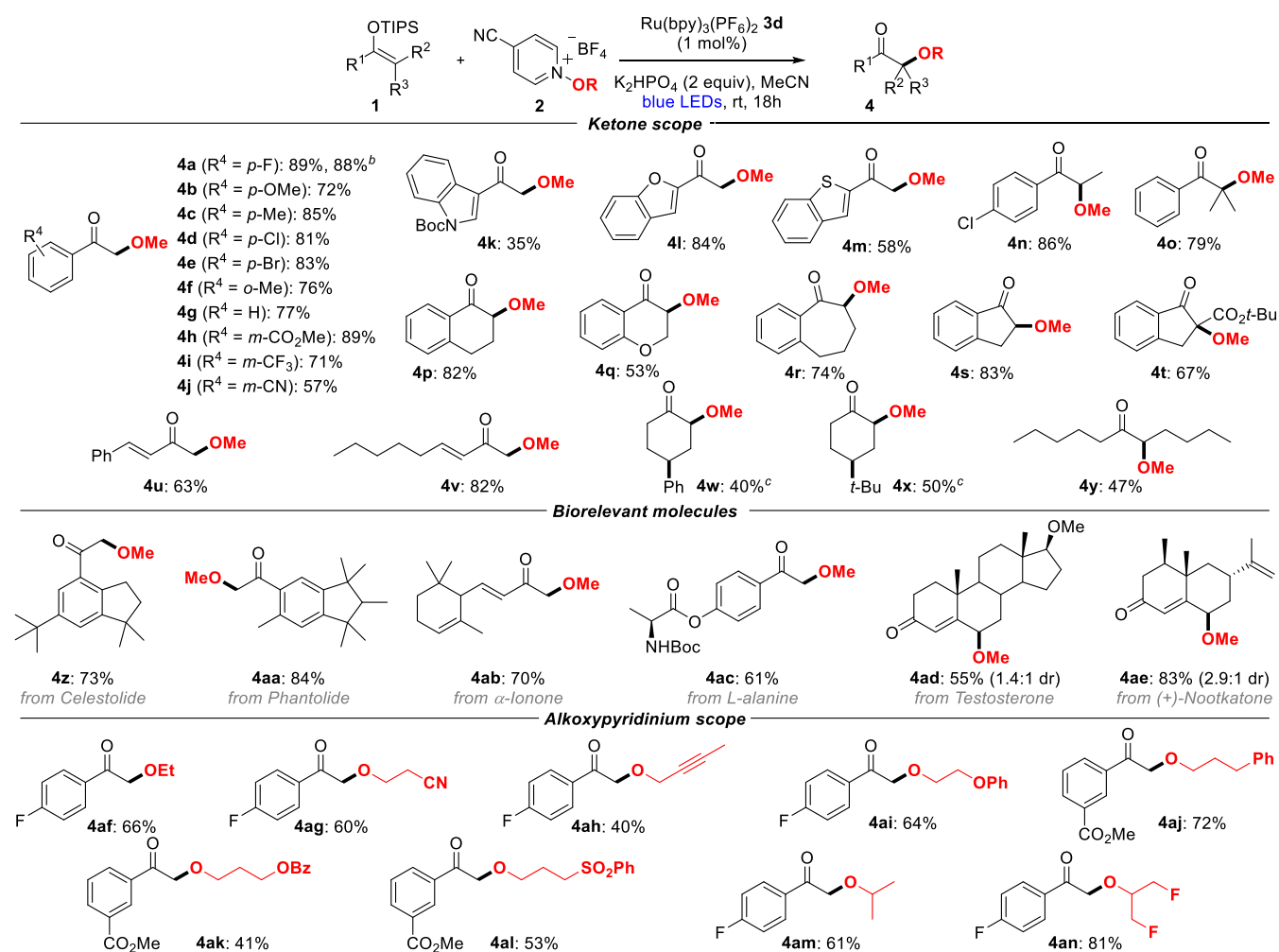
selected as the source of MeO \cdot radical.^{6a,10} We were pleased to see that when this mixture was irradiated with blue LEDs in MeCN, the expected α -methoxylated ketone **4a** was obtained in 27% yield (Table 1, entry 1). However, 4'-fluoroacetophenone, resulting from direct hydrolysis of **1a**, was the major product of this reaction. To prevent the formation of this by-product, a series of organic and inorganic bases were screened (entries 2-9), in which K₂HPO₄ afforded the best result (61% yield, entry 5). Further screening of other parameters (stoichiometry and photocatalyst, entries 10-14) led to the optimal conditions (1.8 equiv of **2a**, with 1 mol% of Ru(bpy)₃(PF₆)₂ **3d**, entry 14), giving product **4a** in 89% isolated yield. Importantly, no trace of by-products resulting from a potential HAT side-reaction could be detected, pointing out the ability for silyl enol ethers to efficiently trap RO \cdot radicals in an intermolecular manner. In addition, no product was observed in the absence of either photocatalyst or light (entries 15-16).

With these optimal reaction conditions in hand, the scope of this novel protocol was then evaluated (Scheme 2). First, various silyl enol ethers **1a-1j** derived from aromatic ketones bearing electron-donating (Me, OMe) or electron-withdrawing groups (F, Cl, Br, CO₂Me, CF₃, CN) in *ortho*, *meta* or *para* positions reacted all smoothly to give the corresponding α -methoxylated ketones **4a-4j** in 57-89% yield. A gram-scale experiment was also successfully carried out and provided 1.48 g of ketone **1a** without any loss of efficiency. Heteroaryl substrates **1k-m** with an indole, benzofuran, or benzothiophene core were also suitable substrates for this reaction and led to the expected products **4k-m** in up to 84% yield. It is also worth noting that the reaction is not limited to methyl ketones, and propiophenone or isobutylphenone derivatives **1n-o** provided the corresponding secondary alkyl ethers **4n-o** in high yields. In addition, cyclic silyl enol ethers **1p-1s** were perfectly tolerated under these mild photoredox conditions and furnished the desired α -methoxylated adducts **4p-4s** in up to 83% yield. The reaction could also be efficiently applied to the synthesis of α -methoxylated β -ketoester **4t** in 67 % yield. Remarkably, the reaction was not limited to aromatic ketones, and 2-silyloxy dienes **1u-1v** derived from aryl- or alkyl-substituted enones gave the desired adducts **4u-4v** in good yields. This novel protocol was also fully compatible with the preparation of cyclic or acyclic aliphatic α -methoxylated ketones **4w-4y**.

To further demonstrate the broad applicability of this new α -alkoxylation process, the late-stage alkoxylation of biorelevant molecules bearing various functional groups was explored. Thus, celestolide, phantolide, α -ionone, and alanine derivatives **1z-1ac** efficiently reacted to afford the desired α -alkoxylated products **4z-4ac** in up to 84% yield. Unlike 2-silyloxy dienes **1u-1v**, 1-silyloxy dienes **1ad** and **1ae** generated from testosterone and (+)-nootkatone reacted exclusively in γ position, without any trace of the α -methoxylated adduct: this selectivity was attributed to the allylic nature of the carbon-centered radical intermediate generated from the γ addition.¹¹

Then, the scope of the reaction with respect to the alkoxy precursor was also explored. *N*-Alkoxyppyridinium salts **2b-2h** bearing a wide range of functionalities (nitrile, alkyne, phenoxy, ester, sulfone) reacted smoothly to provide the targeted alkoxylation ketones **4af-4al** in good yields. The

Scheme 2. Scope of the α -alkoxylation reaction.^a



^aGeneral conditions: **1** (0.2 mmol), **2** (1.8 equiv), **3d** (1 mol%) and K₂HPO₄ (2 equiv) in 2 mL of MeCN irradiated with blue LEDs at rt for 18 h. Given yields are for chromatographically pure isolated products. ^bPerformed on a 10 mmol scale. ^cd.r. > 95:5.

reaction efficiency was not dependent on steric hindrance, as bulkier alkoxy groups such as isopropoxy and 1,3-difluoroisopropoxy were readily incorporated in up to 81% yield (**4am-4an**). Once again, it is worth to mention that no by-product resulting from β -scission or HAT processes could be detected in the crude mixtures.¹²

To demonstrate the synthetic utility of this new photoredox-catalyzed protocol, a two-step, one-pot procedure was developed for the direct α -alkoxylation of ketones. As revealed in Scheme 3a, treatment of ketone **5** with 2,4,6-collidine and triisopropylsilyl triflate provided first the corresponding silyl enol ether **1** without any purification or isolation. This intermediate was then exposed to α -alkoxylation conditions to give the expected α -alkoxylated ketones. This procedure was found to be applicable to the synthesis of ketones **4a,c,l,aj** with good levels of reaction efficiency (57–72% yield).

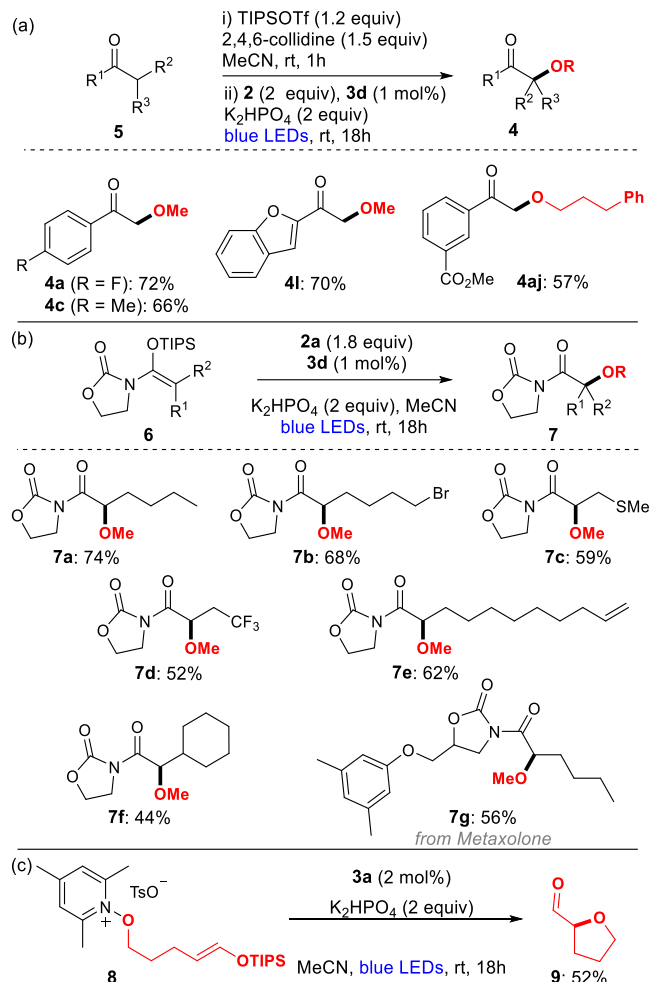
We next sought to examine the applicability of this alkoxylation process to other carbonyl classes, notably silylketene *N,O*-acetals **6** derived from amides. To the best of our knowledge, only one example of C–H α -alkoxylation of amides has been recently reported, based on an “umpolung”

strategy, which highlights the complexity of such transformation.¹³ To our delight, we found that the same reaction conditions could be applied to afford an array of functionalized α -alkoxy amides **7a-g** in good yields (Scheme 3b). Also, given the harsh oxidative conditions of umpolung strategies, aldehydes are quite challenging substrates for C–H α -alkoxylation.¹⁴ We were therefore pleased to see that *N*-alkoxy pyridinium **8** reacted smoothly under our mild photoredox conditions to furnish α -alkoxylated aldehyde **9** in 52% yield (Scheme 3c).¹⁵

As the formation of α -alkoxylated ketones **4** was inhibited in the presence of radical scavengers such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) or in the absence of either photocatalyst or light (see Table 1), we presumed that a radical process was involved. To gain deeper insights into the reaction mechanism, a series of experiments were carried out. First, UV/vis experiments showed that an electron donor–acceptor complex was formed between **2a** and K₂HPO₄ (see ESI for more details).¹⁶ However, the involvement of this EDA complex in a productive reaction pathway is unlikely, as no desired product could be obtained in the absence of photocatalyst (Table 1, entry 15). Then, as outlined in Scheme 4a, luminescence quenching experiments

showed that Ru-photocatalyst **3d** was efficiently quenched by reagent **2a** ($k_{ST} = 2.5 \cdot 10^{-9} \text{ M}^{-1} \cdot \text{s}^{-1}$), compared to substrate **1a** ($k_{ST} = 6.2 \cdot 10^{-7} \text{ M}^{-1} \cdot \text{s}^{-1}$). This, combined with the values of the redox potentials of **2a** and **3d** ($E_{2a} = -0.47 \text{ V vs. SCE}$,¹⁷ $E_{\text{Ru(III)/Ru(II)}^*} = -0.81 \text{ V vs. SCE}$, SCE = Saturated Calomel Electrode), is consistent with an

Scheme 3. (a) One-pot α -alkoxylation. (b-c) α -Alkoxylation of other carbonyls. See ESI for more details.

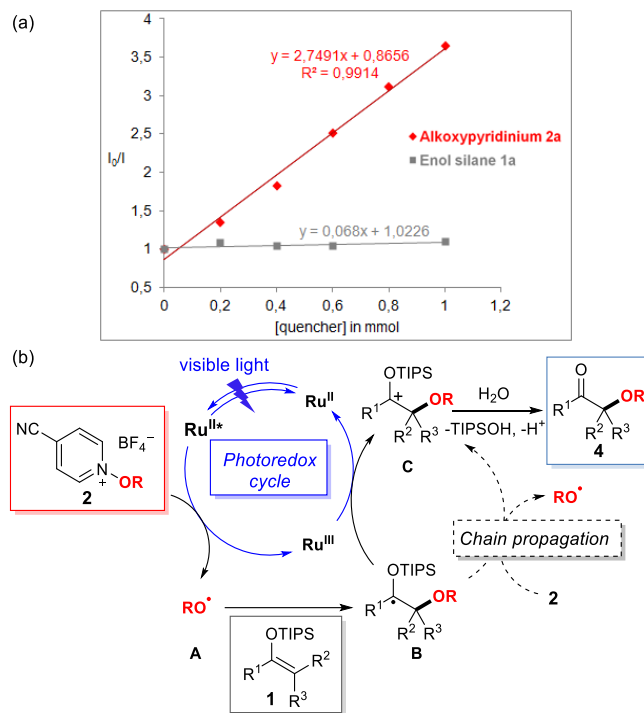


oxidative quenching cycle, in which pyridinium **2a** would be reduced by the excited state of $\text{Ru}(\text{bpy})_3^{3+}$ **3d** (Scheme 4b). This SET reduction would generate the alkoxy radical **A**, which would be trapped by silyl enol ether **1** to lead to α -silyloxy radical **B**. Then, radical **B** is oxidized into carbocation **C**, which finally gives the desired α -alkoxylated adduct **4** after desilylation. The oxidation step leading to intermediate **C** can follow two possible pathways: i) a photocatalytic pathway involving Ru^{III} photocatalyst species; ii) or a radical chain mechanism involving a second molecule of *N*-alkoxy-pyridinium **2**. To distinguish between these two pathways, the quantum yield of the reaction was measured (see ESI for more details). The maximum value $\Phi = 0.74$ indicates that the radical chain process is not the major pathway in this transformation.

In summary, we have developed a new visible-light mediated process that allows for efficient intermolecular α -alkoxylation of various silyl enol ethers and silylketene *N,O*-acetals derived from a wide array of functionalized ketones

and amides. Importantly, the synthetic value of this method was further demonstrated by the late-stage functionalization of more complex biorelevant molecules, and a one-pot protocol was readily applied to the direct α -alkoxylation of carbonyl compounds. Extension to catalytic enantioselective α -alkoxylation processes is currently under study and will be reported in due course.

Scheme 4. Mechanistic investigations.



^aLuminescence quenching experiments. Stern Volmer plots $I_0/I = f([\text{quencher}])$ using **1a** or **2a** as the quencher. ^bPlausible mechanism.

ASSOCIATED CONTENT

Detailed experimental procedures, characterization data, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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