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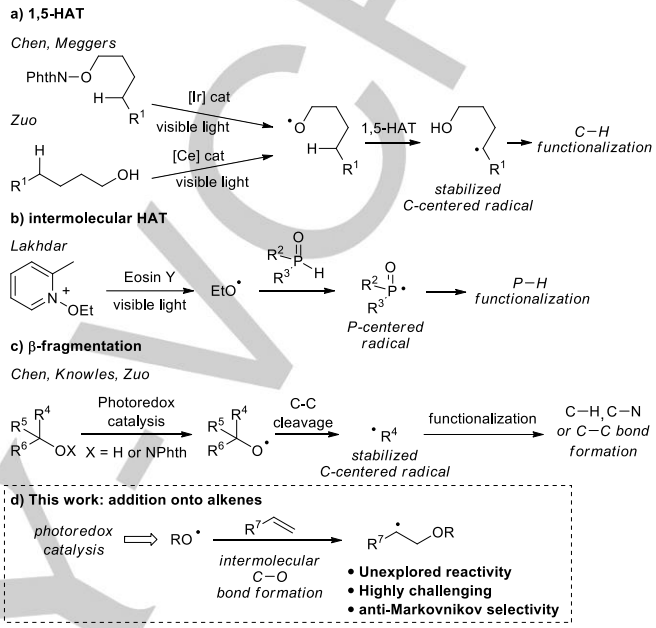
Alkoxyl Radicals Generated under Photoredox Catalysis: A Strategy for anti-Markovnikov alkoxylation reactions

Anne-Laure Barthelemy,[a] Béatrice Tuccio,[b] Emmanuel Magnier[a] and Guillaume Dagousset*[a]

Abstract: We report herein a novel photoredox-catalyzed approach for ether synthesis, involving alkoxyl radicals generated from N-alkoxypyridinium salts. A wide range of alkenes are smoothly difunctionalized in an anti-Markovnikov fashion, affording various functionalized alkyl alkyl ethers. Notably, this mild process tolerates a large number of functional groups and is efficiently carried out under batch and flow conditions. Importantly, electron paramagnetic resonance (EPR) experiments by spin trapping are carried out in order to characterize the radical intermediates involved in this radical/cationic process.

Alkoxyl radicals (RO·) are versatile intermediates, which not only play a pivotal role in many biological processes but also are key chemical species in a wide variety of organic transformations.[1] Many strategies have been reported these last decades to generate these highly reactive species, using a wide number of RO· precursors such as nitrites,[2] hypohalites,[3] peroxides,[4] sulfenyl ethers,[5] N-alkoxypyridine-2-thiones [6] or N-alkoxyphthalimides.[7] However, these sources of alkoxyl radicals suffer from several major limitations: they are either toxic/unstable, or require the use of stoichiometric amounts of radical initiators (typically Bu_3SnH/AIBN mixture), or need harsh reaction conditions (UV light irradiation, high temperatures) which are incompatible with many sensitive functional groups.

To circumvent these issues, photoredox catalysis has very recently been used as a powerful and eco-friendly means to generate alkoxyl radicals.[8,9] Notably, the groups of Chen[10] and Meggers[11] reported the use of N-alkoxyphthalimides for selective C(sp^3)–H functionalization thanks to the ability of RO· radicals to perform 1,5-hydrogen atom transfer (HAT). A similar 1,5-HAT reactivity was later exploited by Zuo and co-workers for the δ-selective functionalization of alkanols (Scheme 1a).[12] Furthermore, the intermolecular HAT reactivity of alkoxyl radicals was used by Lakhdar and co-workers for the P–H functionalization of phosphine oxides (Scheme 1b).[13] In addition, the propensity of RO· radicals to easily undergo β-fragmentation was also exploited by the groups of Chen,[14] Knowles,[15] and Zuo[16] who reported efficient C–C bond cleavage and further functionalization of the resulting C-centered radical (Scheme 1c). It is worth noting that in all these examples, N-alkoxyphthalimides or alcohols have all been specifically designed. Indeed, the RO· radical intermediate reacts only *via* 1,5-HAT or β-fragmentation because of its predisposition to generate a highly stabilized C–centered radical (either a radical in α position to an heteroatom, or a benzylic radical, or a tertiary radical). For other less specific RO· radicals, we envisioned that they could be trapped in an intermolecular manner by an appropriate radical scavenger, such as an alkene, before any



Scheme 1. Different reactivities of alkoxyl radicals generated under photoredox catalysis. NPhth = phthalimido.

HAT or β-fragmentation processes occurred (Scheme 1d). If such type of reactivity has been reported for other oxygen-centered radicals such as nitroxide radicals,[17] to the best of our knowledge in the case of alkoxyl radicals, it has not been used in preparative and synthetically useful organic synthesis.[3,4,18] We wish to report herein the first efficient synthesis of ethers involving alkoxyl radicals generated under photoredox catalysis. This method is of high interest, as it will lead to the preparation of functionalized ethers with anti-Markovnikov regioselectivity, which is currently a significant challenge in organic chemistry.[19] We first chose to focus on the hydroxyalkoxylation of alkenes as a model reaction (Table 1). Such photoredox-catalyzed three-component difunctionalization reactions are indeed of high interest and enable the one-pot synthesis of adducts of great diversity and complexity from readily available building blocks.[20] Moreover, compared to the well-known dihydroxylation of olefins,[21] such hydroxyalkoxylation process usually requires a two-step protocol, as one-pot procedures generally lead to poor chemo- and/or regioselectivities.[22] To this end, we started screening potential sources of methoxyl radical in the presence of the strongly reducing photocatalyst *fac*-Ir(ppy)$_3$ **2a**. When alkene **1a** was treated with 2 mol% of **2a** and with N-methoxyphthalimide **3a** as a potential source of MeO· radical, no desired product **4a** could be detected (entry 1). We then decided to turn our attention to N-alkoxypyridinium salts.[13] These reagents are efficiently prepared in gram-scale from the corresponding readily available pyridine N-oxides (see the

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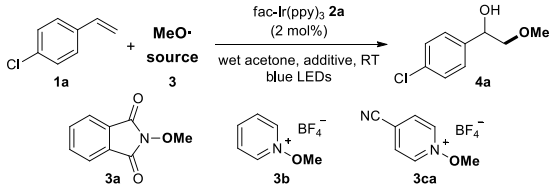
Table 1. Survey of reaction conditions for the photoredox-catalyzed hydroxyalkoxylation of alkene **1a**.



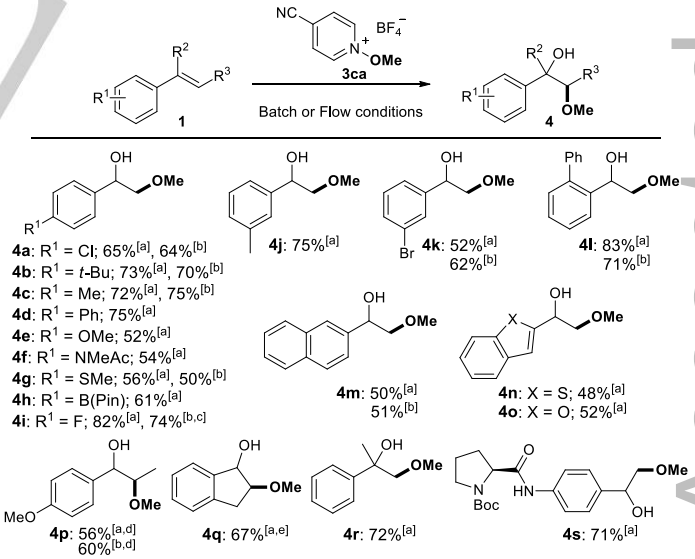
Entry	MeO· source	Additive	Yield [%][a,b]
1	**3a**	none	0
2	**3b**	none	24
3	**3b**	CsF	37
4	**3b**	2,6-lutidine	32
5	**3b**	$NaH_2PO_4{\cdot}2H_2O$	40
6	**3ca**	$NaH_2PO_4{\cdot}2H_2O$	44
7[c]	**3ca**	$NaH_2PO_4{\cdot}2H_2O$	60
8[d]	**3ca**	$NaH_2PO_4{\cdot}2H_2O$	50
9[c,e]	**3ca**	$NaH_2PO_4{\cdot}2H_2O$	67 (65)[f]
10[g]	**3ca**	none	(64)[f]
11[c,h]	**3ca**	$NaH_2PO_4{\cdot}2H_2O$	0
12[c,i]	**3ca**	$NaH_2PO_4{\cdot}2H_2O$	0

[a] General conditions: **1a** (0.10 mmol), **3** (0.20 mmol), **2a** (0.02 equiv) in 1 mL of wet acetone irradiated at RT for 24 h. [b]Yields determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [c] With 0.20 mmol of **1a** and 0.10 mmol of **3** for 36 h. [d] With 0.15 mmol of **1a** and 0.10 mmol of **3** for 36 h. [e] With 1 mol% of **2a**. [f] Yields referred to chromatographically pure product in parentheses. [g] Using flow conditions, with 3 mol% of **2a**. See the Supporting Information for more details. [h] In the dark. [i] Without **2a**.

Supporting Information for the synthesis of a variety of N-alkoxypyridinium salts bearing various electron-donating or withdrawing groups). To our delight, when N-methoxypyridinium salt **3b** was tested, the expected three-component adduct **4a** was obtained in 24% NMR yield with perfect anti-Markovnikov-type regioselectivity after 24 h of irradiation with blue LEDs (entry 2), albeit with incomplete conversion. Encouraged by this promising result, the reaction conditions were next optimized (entries 3-9, see the Supporting Information for more details). Notably, the addition of a base such as NaH_2PO_4 enabled the reaction to go to completion within 36 h, probably by assisting the nucleophilic attack of water. Furthermore, the yield was improved by using 4-cyano substituted N-methoxypyridinium salt **3ca**, and the hydroxymethoxylated product **4a** was isolated in 65% yield (entry 9). In addition, in order to accelerate this alkoxylation process, we also optimized this novel reaction with the use of continuous-flow techniques, which are perfectly well adapted to photochemical transformations: indeed, they provide a more homogeneous irradiation of the reaction mixture, enhanced mass transfer characteristics, and allow performing scale-up experiments.[23] Under slightly modified reaction conditions (entry 10), we were pleased to see that the hydroxyalkoxylation of **1a** could be carried out with a residence time of 1 h at 25 °C (see the Supporting Information for more details). Remarkably, under these conditions, the assistance of a base was not required to achieve complete conversion, pointing out the high efficiency of this continuous-flow process.

With these optimized conditions in hand, the scope of this novel photocatalyzed hydroxyalkoxylation was next investigated in batch and in continuous flow and the results are summarized in Scheme 2. A wide range of styrene derivatives were well tolerated. Notably, various functionalities, such as halogens, ethers, thioethers, amides, carbamates, or boronic esters, were compatible with the mild reaction conditions, affording the corresponding hydroxymethoxylated compounds **4a-4m** in 50-83% yield.[24] Vinyl-substituted heteroarenes **1n**-**o** also reacted smoothly during this photocatalyzed process. Interestingly, this three-component reaction was successfully broadened to α- and β-substituted styrenes **1p-r**, providing the corresponding alkoxylated alcohols **4p-r** in up to 72% yield. A key feature of photoredox-catalyzed transformations consists of the late-stage functionalization of complex small molecules, which is a very important tool in modern drug discovery. To this end, proline-derived alkene **1s** was also smoothly converted into highly functionalized adduct **4s** in 71% yield. In addition, a gram-scale experiment was performed for the synthesis of adduct **4i** without any decrease in yield, showing the practicity and efficiency of continuous-flow techniques.

Although our attempts to synthesize tertiary N-alkoxypyridinium salts (e.g. R = *t*-Bu, Scheme 3) were all unsuccessful, it is worth noting that other N-alkoxypyridinium salts **3cb-3cl** derived from primary or secondary alkoxy groups with various functionalities (halogen, azido, cyano, ester, trifluoromethyl, sulfonyl) were also suitable partners and led to the desired adducts **4t-4ad** in good yields (Scheme 3). In particular, N-alkoxypyridinium **3cj** bearing an alkyne moiety was successfully employed to afford the



Scheme 2. Scope of alkenes. Yields referred to chromatographically pure product. [a] Batch conditions: alkene **1** (0.2 mmol), **3ca** (0.1 mmol), **2a** (1 mol%), $NaH_2PO_4{\cdot}2H_2O$ (0.1 mmol) in wet acetone (1 mL) irradiated with blue LEDs at RT for 36 h. [b] Flow conditions: alkene **1** (0.2 mmol), **3ca** (0.1 mmol), **2a** (3 mol%), in acetone/CH_2Cl_2 mixture (5:1, 2 mL) irradiated with blue LEDs with a flow rate of 0.15 mL.min^{-1} at 25°C. [c] With 4 mmol of **3ca**. [d] d.r. = 1.7:1. [e] d.r. = 2:1. d.r. = diastereomeric ratio.

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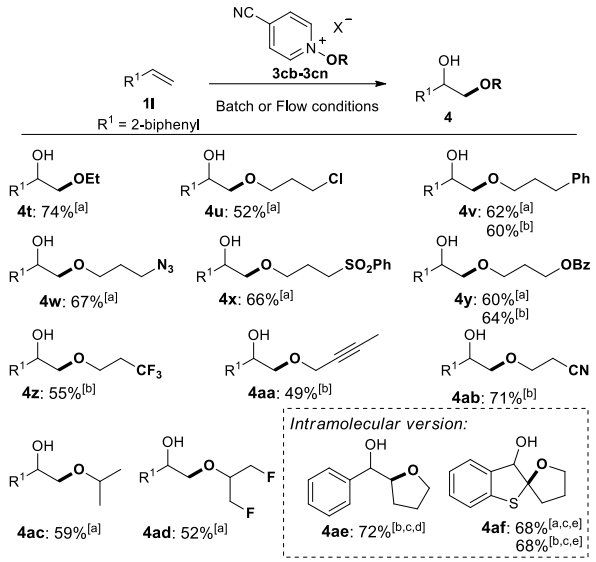
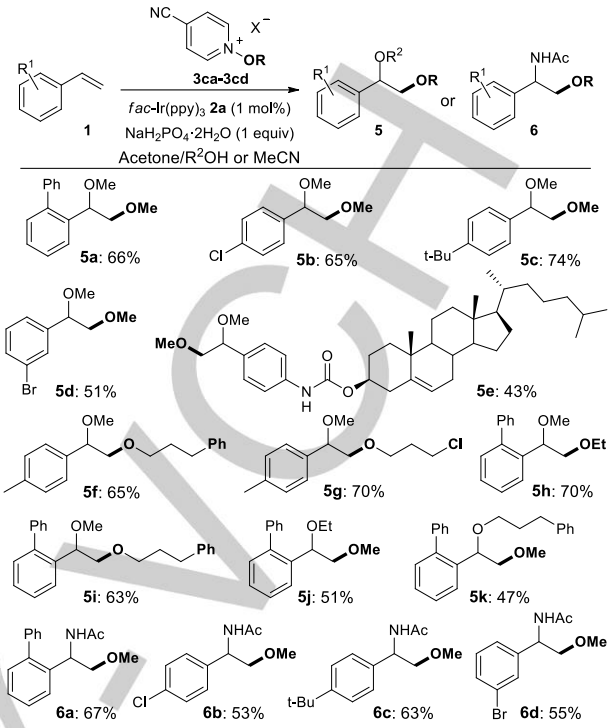


Scheme 3. Scope of N-alkoxypyridinium salts. Yields referred to chromatographically pure product See Scheme 2 for conditions [a] and [b]. [c] Reaction performed without alkene **1l**. [d] d.r. = 1.1:1. [e] d.r. = 2.3:1. X = BF_4 or OTf.



Scheme 4. Dialkoxylation and aminoalkoxylation. See the Supporting Information for details. Yields referred to chromatographically pure product.

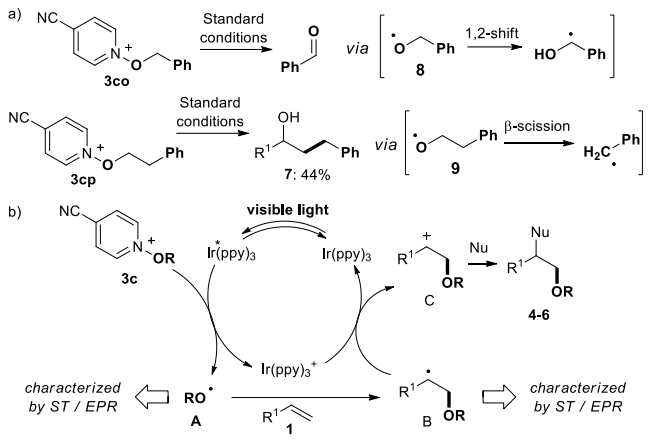
corresponding compound **4aa**, pointing out the high chemoselectivity of this photoredox-catalyzed three-component process. Finally, this hydroxyalkoxylation process was also readily carried out in an intramolecular fashion with N-alkoxypyridinium salts **3cm-3cn**, providing the corresponding cyclic ethers **4ae-4af** in good yields.

In order to demonstrate the versatility of this novel radical approach towards ether synthesis, we next focused on dialkoxylation of alkenes. To the best of our knowledge, in previous reports on such transformation,[25] the alkoxyl source is always an alcohol which is used as solvent. This leads to two main drawbacks: i) Such processes have been mainly limited to methoxy or ethoxy groups, and have not been extended to more complex alkoxy groups; ii) three-component dialkoxylation processes with two different alkoxy groups have not been reported yet. Our method involving alkoxyl radicals under photoredox catalysis would provide a solution to both these limitations. Pleasingly, by adding an alcohol in the reaction mixture, our methodology was successfully broadened to the synthesis of a wide range of dialkoxylated adducts **5a-k** bearing various functional groups (Scheme 4). Once again, such process was readily applied to the late-stage functionalization of complex molecules such as cholesterol-derived alkene **1v**, without any degradation of its tri-substituted C–C double bond. It is also worth noting that unsymmetrical regioisomers **5h** and **5j** as well as regioisomers **5i** and **5k** were for the first time efficiently prepared starting from the same substrate **1l**.

Finally, we decided to use acetonitrile as both the solvent and the nucleophile, as it is known to easily trap carbocation intermediates (Ritter-type reaction). To our delight, this photoredox-catalyzed aminoalkoxylation reaction was efficiently applied to functionalized alkenes, affording products **6a-d** in good yields.

To study the mechanism of these alkoxylation reactions, the following control experiments were performed. No reaction took place in the absence of irradiation and/or *fac*-Ir(ppy)$_3$ **2a** (see Table 1, entries 11-12). Moreover, the formation of **4-6** was inhibited in the presence of radical scavengers such as TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) or O_2, suggesting that a radical process is involved in this reaction. Furthermore, when N-alkoxypyridinium salts **3co** and **3cp** were subjected to the optimal reaction conditions, benzaldehyde and compound **7** were isolated as major products, respectively (Scheme 5a). These compounds are most probably resulting from 1,2-H shift and β-scission of the respective alkoxyl radical intermediates **8** and **9**, which is once again in favour of a radical mechanism. In addition, various spin trapping / electron paramagnetic resonance (ST/EPR) experiments were carried out, and allowed verifying the formation of RO· radicals without ambiguity (see the Supporting Information for more details). Based on these experiments, the most plausible mechanism is proposed in Scheme 5b. First, N-alkoxypyridinium salt **3c** (E_{red} (**3ca**) = –0.47 V vs. SCE)[26] is reduced by the excited state of *fac*-Ir(ppy)$_3$ **2a** (–1.73 V vs. SCE), generating RO· **A**. This radical can then add onto alkene **1**, leading to a carbon-centered radical **B** stabilized in benzylic position. It is worth noting that alkyl substituted alkenes, such as 6-phenyl-1-hexene or methylenecyclohexane, which are less capable of stabilizing radical intermediates, were not suitable partners for this transformation. Subsequently, SET oxidation of **B** by Ir(ppy)$_3^+$ generates the corresponding carbocation **C** stabilized in benzylic position. Final trapping with either water, alcohol or acetonitrile, provides the corresponding products **4-6**.

In summary, we have developed a novel strategy for ether



Scheme 5. a) Control experiments. b) Proposed mechanism. R^1 = 2-biphenyl.

synthesis involving alkoxyl radicals generated from N-alkoxypyridinium salts under photoredox catalysis. Three new types of difunctionalization of alkenes (hydroxyalkoxylation, dialkoxylation, and aminoalkoxylation) with perfect anti-Markovnikov-type regioselectivity have been successfully developed, which tolerate a wide range of functional groups and are amenable to gram scale synthesis thanks to continuous-flow techniques. Other ether syntheses involving alkoxyl radicals are currently under investigation in our laboratory and will be reported in due course.

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Keywords: alkoxyl radicals • photoredox catalysis • anti-Markovnikov selectivity • ethers • alkoxypyridinium salts

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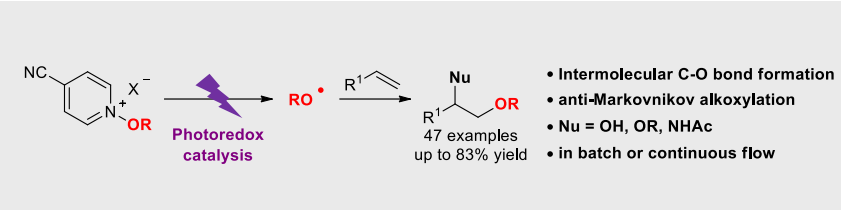

Alkoxyl radicals generated under visible light photoredox catalysis from N-alkoxypyridinium salts were for the first time efficiently trapped by alkenes in an intermolecular fashion, using either batch or flow conditions. This alkoxylation strategy enabled the access to a wide variety of functionalized alkyl alkyl ethers, thanks the difunctionalization of alkenes with perfect anti-Markovnikov selectivity.

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Alkoxyl Radicals Generated under Photoredox Catalysis: A Strategy for anti-Markovnikov alkoxylation reactions