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Highly Selective $\gamma$-Alkoxylation, $\gamma$-Amination and $\gamma$-Alkylation of Unbiased Enals by Means of Photoredox Catalysis

Camille Banoun,a Flavien Bourdreux,a Guillaume Dagousset+a

Abstract. We report herein a general and highly selective $\gamma$-functionalization protocol under visible light irradiation. This mild radical approach enables to expand the scope of application to unbiased enals and to introduce a wide variety of alkoxy, amino and alkyl functionalities in the $\gamma$ position with complete regioselectivity. Classical methodologies of organic synthesis generally involve functionalization at the most reactive center of an organic compound. By comparison, remote functionalization allows for a selective reaction to proceed at a distal and less reactive position.1 This powerful concept has notably been used for the $\gamma$-functionalization of $\alpha,\beta$-unsaturated.2 Such remote functionalization was notably pioneered by Mukaiyama’s work on vinylogous aldol reaction, enabling the access to $\delta$-alkoxy-$\alpha,\beta$-unsaturated aldehydes.3 Since then, the most significant achievement in this field has most probably been the development of dienamine catalysis (Scheme 1a).4 While this powerful catalytic mode enables to directly functionalize enals in the $\gamma$ position in an enantioselective manner, it still faces two main limitations: i) except for very rare examples, a branching substitution pattern in $\alpha$ position of the enal substrate is generally required to achieve high level of enantioselectivity (by controlling the geometry of the dienamine) as well as high level of $\gamma$-regioselectivity (by hindering the $\alpha$ position);5 ii) Dienamine catalysis is only efficient with specific C-centered electrophiles, such as activated alcohols or ketones,5 and methods to create a new C(sp3)–Heteroatom bond in $\gamma$ position are highly needed: indeed, to the best of our knowledge, only one N-centered electrophile (azodicarboxylate) was successfully used for the formation of $\gamma$-C(sp3)–N bonds, via a specific [4+2] cycloaddition pathway.6 Importantly, a dienamine-catalyzed $\gamma$-oxygenation of enals is still unknown to date.7 To overcome these limitations, we envisaged a new radical-based strategy in which a $\cdot$Y radical would selectively add onto the $\gamma$ position of silylated dienol ether 1. Indeed, due to its allylic nature, radical intermediate I resulting from this $\gamma$-addition would be more stable than intermediate II arising from $\alpha$-addition (Scheme 1b).8 Similar radical approaches under dienamine-catalyzed conditions have only been scarcely

Scheme 1: Overview of $\gamma$-functionalizations of enals.

a) Dienamine-catalyzed $\gamma$ functionalization of enals

b) This work: radical remote $\gamma$ functionalization of enals

To overcome these limitations, we envisaged a new radical-based strategy in which a $\cdot$Y radical would selectively add onto the $\gamma$ position of silylated dienol ether 1. Indeed, due to its allylic nature, radical intermediate I resulting from this $\gamma$-addition would be more stable than intermediate II arising from $\alpha$-addition (Scheme 1b). Similar radical approaches under dienamine-catalyzed conditions have only been scarcely
studied until recently, and are mostly limited to C(sp^3)–C bond formation and to α-branched enals. Although not enantioselective, our strategy would unlock the challenging α/γ-regioselectivity issue in the case of unbiased α-unbranched enals. Moreover, as our hypothesis does not depend on the nature of the ·Y radical, it would pave the way for many previously inaccessible γ-functionalizations of enals, and more specifically γ-heterofunctionalization such as γ-oxygenation and γ-amination reactions.

We first started our investigations into the feasibility of a selective dieneamine-catalyzed process for the γ-oxygenation of enals. Unfortunately, as in previous works,\textsuperscript{7} all our efforts were unsuccessful to afford the desired γ-functionalized product, even in the case of α-hindered enals. These results showed that dieneamine catalysis cannot be the solution to all the problems faced in the field of γ-functionalization of enals. With our initial radical strategy in mind, and based on our recent works on the generation of alkoxyl radicals under photoredox catalysis,\textsuperscript{11} we then decided to study the completely unknown photocatalyzed synthesis of γ-alkoxylation of silylated dienol ether 3a from the corresponding triisopropylsilyl (TIPS) dienol ether 1a and N-methoxypyridinium salt 2a (Table 1). Pleasingly, a good yield of 71% was obtained when using 2 mol% of Ir(ppy)\textsubscript{3} as the photocatalyst, MeCN as the solvent, and K\textsubscript{2}HPO\textsubscript{4} as the base (Entry 1). Importantly, a perfect γ-selectivity was observed, which validated our working hypothesis. Other photocatalysts or solvents were tested but gave lower yields (Entries 2-4). It is worth noting that substrate 1a is sensitive to acidic conditions, and that the presence of a base in the reaction medium is needed in order to avoid hydrolysis of 1a into (E)-2-dodecenal (Entries 5-7). The base could also participate in an EDA complex with N-alkoxy pyridinium 2a,\textsuperscript{11c,12} however this EDA complex is probably only a minor reaction pathway, as compound 3a was produced in merely 6% yield in the absence of any photocatalyst (Entry 9). Finally, a control experiment showed that no product was formed in the absence of visible light (Entry 8).

Using the optimized reaction conditions (Table 1, Entry 1), we then tested the generality of this new photocatalytic γ-alkoxylation process (Scheme 2). A variety of unbiased α-unbranched γ-methoxy enals 3a-3e bearing some functionalities such as alkene, ester or phthalimide group, were successfully prepared with high efficiency (70-75% yield). Although α-phenyl substrates gave a complex mixture, α-alkyl substrates were compatible with the reaction conditions, yielding products 3f-3g with similar complete regioselectivity. It is worth noting that the terminal C=C double bond of natural monoterpenoid (S)-perillaldehyde remained untouched, highlighting the chemoselective nature of the process. Then, we evaluated the scope of the alkoxyl radicals that could be intercepted by silyl dienol ether 1a. Pleasingly, N-alkoxy pyridinium salts with a large array of functional groups

(sulfone, ether, chloro, ester) were all efficiently engaged in the mild photoredox-catalyzed reaction, providing the corresponding adducts 3h-3k in up to 71% yield. Remarkably, the use of a secondary alkoxyl radical led to the desired γ-alkoxylated product 3l in a good yield of 65%.

Pyridinium salts have recently emerged as efficient scaffolds to generate radicals under photoredox catalysis.\textsuperscript{13} We therefore decided to examine the applicability of this protocol to N-aminopyridinium salts. To our delight, we found that under similar reaction conditions N-centered radicals (sulfonamidyld, carbamimidyl, as well as phthaloyl-derived radicals) were all smoothly incorporated in γ position, furnishing enals 4a-g in a completely regioselective manner. Interestingly, more complex natural compounds were also suitable substrates, as exemplified by γ-aminated (1R,−)−myrtenal adduct 4d obtained in 60% yield.

On the strength of our findings for γ-alkoxylation and γ-amination reactions, we next attempted to apply our protocol to the preparation of γ-alkylated enals. Pleasantly, when 1.5 equiv. of diethyl bromomalonate 5a was used as the source of C-centered radical, the desired adduct 6a was produced in 75% yield. A large array of other unbiased γ-alkylated enals 6b-6i were readily obtained in up to 84% yield, without any trace of the α-adduct. Unsurprisingly, the same γ-selectivity was observed in the case of α-substituted enals 6j-I. It is worth noting that the late-stage functionalization of more complex molecules such as (S)-(+)-perillaldehyde, (1R,−)−myrtenal, or L-tyrosine derivative proceeded smoothly (6m-o), pointing out the broad applicability of this new γ-alkylation process. Finally, other C-centered radicals generated from methyl trichloroacetate 5b, bromoacetanitride 5c, 2-iodo-1,1,1-trifluoroethane 5d, 2-bromo-2-nitropropane 5e, or 2-bromoacetophenone derivatives 5f-I could also be selectively

\textbf{Table 1: Optimization of the γ-methoxylation of silylated dienol ether 1a.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Yield (%)\textsuperscript{a,b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>75 (71)\textsuperscript{d}</td>
</tr>
<tr>
<td>2</td>
<td>Ru(bpy)\textsubscript{3}(PF\textsubscript{6})\textsubscript{2} instead of Ir(ppy)\textsubscript{3}</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>Eosin Y instead of Ir(ppy)\textsubscript{3}</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Acetone instead of MeCN</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>K\textsubscript{2}CO\textsubscript{3} instead of K\textsubscript{2}HPO\textsubscript{4}</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>NaH\textsubscript{2}PO\textsubscript{4} instead of K\textsubscript{2}HPO\textsubscript{4}</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>No base</td>
<td>34\textsuperscript{d}</td>
</tr>
<tr>
<td>8</td>
<td>No light</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>No photocatalyst</td>
<td>6</td>
</tr>
</tbody>
</table>

\textsuperscript{a}General conditions: 1a (0.2 mmol), 2a (0.36 mmol), Ir(ppy)\textsubscript{3} (2 mol%) and K\textsubscript{2}HPO\textsubscript{4} (2 equiv) in 2 mL of MeCN irradiated with 5W blue LEDs at r.t. for 18 h. \textsuperscript{b}Yields determined by \textsuperscript{1}H NMR spectroscopy using 1,4-dicyanobenzene as an internal standard. \textsuperscript{c}Yield into brackets refers to chromatographically pure product. \textsuperscript{d}59% of (E)-2-dodecenal was formed during the reaction.
incorporated in ϒ position, leading to the corresponding enals 6p-ω in up to 81% yield. To demonstrate the synthetic utility of this ϒ-regioselective process, a 4-mmol scale experiment was performed with substrate 1a and reagent 5a. After 18h of irradiation, 450 mg of ϒ-functionalized enal 6a could be isolated, showing the simplicity to scale up the process (Scheme 3a). In addition, a two-step, one-pot procedure was developed for the direct ϒ-functionalization of enals: treatment of 2-dodecenal with 2,4,6-collidine and trisopropylsilyl triflate provided first the corresponding silylated dieno 1a without any purification or isolation. This intermediate was then exposed to photocatalyzed ϒ-alkylation conditions with 5a, giving the desired α-alkylated enal 6a without any loss of efficiency. We then decided to study the mechanism of this new ϒ-functionalization reaction. As both light and IrIII catalyst were required, a radical-based photocatalytic pathway was hypothesized. Indeed, given the redox potential of the excited
state of Ir(ppy)$_3$ (E = −1.73 V vs SCE), a SET reduction of reagents 2 or 5 (for instance, E$^{red}_{red}(2a) = −0.47$ V vs SCE; 14 and E$^{red}_{red}(5a) = −0.62$ V vs SCE) should likely occur to generate the corresponding Y-radical. This assumption was corroborated by luminescence quenching experiments (see ESI for more details), which indicated that radical sources 2 and 5 efficiently quenched the luminescence of excited Ir*-(ppy)$_3$. The resulting Y-radical then adds selectively on the γ-position of substrate 1, in order to afford a more stabilized allylic radical intermediate A. Subsequent SET oxidation of A into the corresponding carbocation B, followed by a desilylation step, leads to the desired γ-functionalized products 3–4,6 (Scheme 3b). In addition, the quantum yield of the reaction (Φ < 0.45, see ESI for more details) indicated that although a short-chain mechanism involving the SET reduction of 2/5 by A cannot be completely ruled out, the photocatalytic process was most probably the major productive pathway of this reaction.

In summary, we have developed a versatile α/γ-functionalization of enals. Importantly, this new visible-light mediated process operates with perfect site-selectivity even in the challenging case of unbiased α-unbranched enals, and is applicable to the synthesis of a wide range of γ-alkoxylated, γ-aminated, and γ-alkylated enals which cannot be prepared under otherwise conventional electrophilic conditions. Further developments in the field of remote functionalization are currently underway and will be reported in due course.

**Conflicts of interest**

There are no conflicts to declare.

Acknowledgements

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**Notes and references**

10. A similar photocatalyzed γ-amination of enones and enals was reported during the submission of this manuscript: K. F. Szabó, K. Goliszewska, J. Szurmak, K. Rybicka–Jasińska and D. Gryko, Org. Lett., 2022, 24, 8120.