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Camille Banoun, Flavien Bourdreux, Guillaume Dagousset. Highly selective γ -alkoxylation, γ -amination and γ -alkylation of unbiased enals by means of photoredox catalysis. *Chemical Communications*, 2023, 59 (6), pp.760-763. 10.1039/d2cc05749b . hal-03961871

HAL Id: hal-03961871

<https://hal.science/hal-03961871>

Submitted on 2 Feb 2023

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Highly Selective γ -Alkoxylation, γ -Amination and γ -Alkylation of Unbiased Enals by Means of Photoredox Catalysis

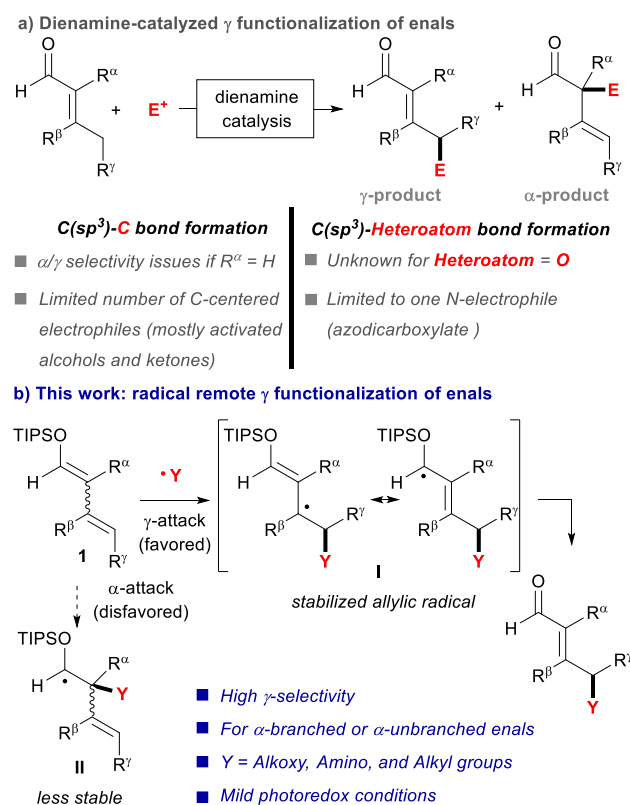
Camille Banoun,^a Flavien Bourdreux,^a Guillaume Dagousset*^a

Abstract. We report herein a general and highly selective γ -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 γ 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 γ -functionalization of α,β -unsaturated.² Such remote functionalization was notably pioneered by Mukaiyama's work on vinylogous aldol reaction, enabling the access to δ -alkoxy- α,β -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 γ position in an enantioselective manner, it still faces two main limitations: i) except for very rare examples, a branching substitution pattern in α 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 γ -regioselectivity (by hindering the α 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 γ position are highly needed: indeed, to the best of our knowledge, only one N-centered electrophile (azodicarboxylate) was successfully used for the formation of γ -C(sp³)-N bonds, *via* a specific [4+2] cycloaddition pathway.⁶ Importantly, a dienamine-catalyzed γ -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 γ position of silylated dienol ether **1**. Indeed, due to its allylic nature, radical intermediate **I** resulting from this γ -addition would be more stable than intermediate **II** arising from α addition (Scheme 1b).⁸ Similar radical approaches under dienamine-catalyzed conditions have only been scarcely

Scheme 1: Overview of γ -functionalizations of enals.

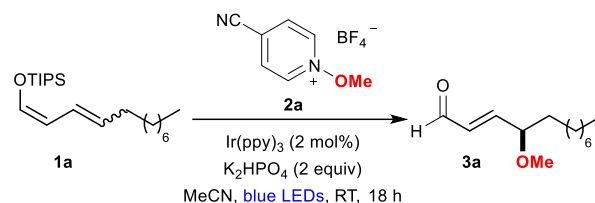


studied until recently, and are mostly limited to C(sp³)-C bond formation and to α -branched enals.^{9,10} Although not enantioselective, our strategy would unlock the challenging α/γ regioselectivity issue in the case of unbiased α -unbranched enals. Moreover, as our hypothesis does not depend on the nature of the $\cdot Y$ 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 dienamine-catalyzed process for the γ -oxygenation of enals. Unfortunately, as in previous works,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 dienamine 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 alkoxy radicals under photoredox catalysis,¹¹ we then decided to study the completely unknown photocatalyzed synthesis of γ -alkoxylated enal **3a** from the corresponding triisopropylsilyl (TIPS) dienol ether **1a** and *N*-methoxyppyridinium salt **2a** (Table 1). Pleasingly, a good yield of 71% was obtained when using 2 mol% of Ir(ppy)₃ as the photocatalyst, MeCN as the solvent, and K₂HPO₄ 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*-alkoxyppyridinium **2a**,^{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 photochemical 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*)-perrilaldehyde remained untouched, highlighting the chemoselective nature of the process. Then, we evaluated the scope of the alkoxy radicals that could be intercepted by silyl dienol ether **1a**. Pleasingly, *N*-alkoxyppyridinium salts with a large array of functional groups

Table 1: Optimization of the γ -methoxylation of silylated dienol ether **1a**.



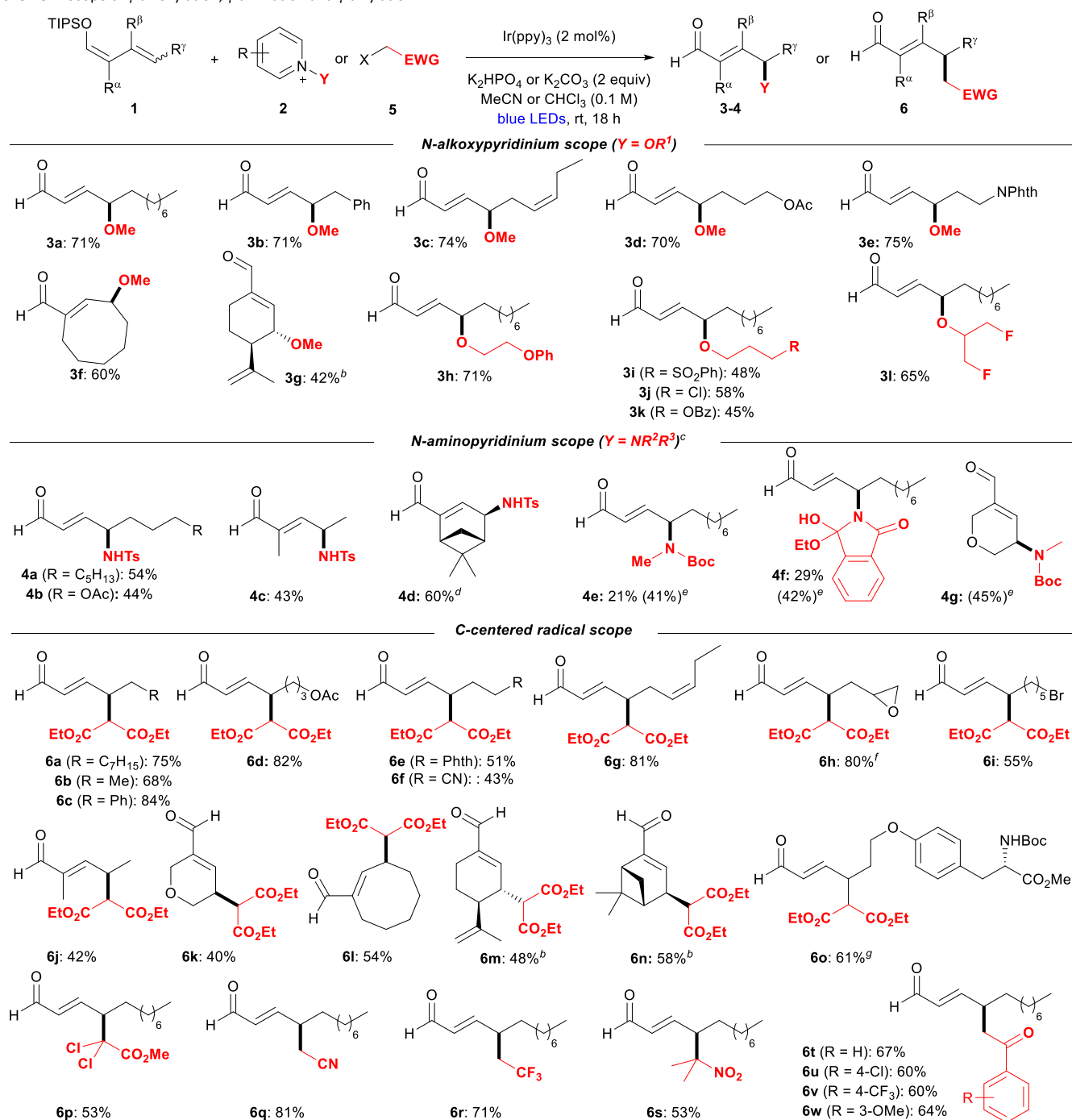
Entry	Deviation from standard conditions	Yield (%) ^{a,b}
1	None	75 (71) ^c
2	Ru(bpy) ₃ (PF ₆) ₂ instead of Ir(ppy) ₃	59
3	Eosin Y instead of Ir(ppy) ₃	33
4	Acetone instead of MeCN	11
5	K ₂ CO ₃ instead of K ₂ HPO ₄	25
6	NaH ₂ PO ₄ instead of K ₂ HPO ₄	41
7	No base	34 ^d
8	No light	0
9	No photocatalyst	6

^aGeneral conditions: **1a** (0.2 mmol), **2a** (0.36 mmol), Ir(ppy)₃ (2 mol%) and K₂HPO₄ (2 equiv) in 2 mL of MeCN irradiated with 5W blue LEDs at r.t. for 18 h. ^bYields determined by ¹H NMR spectroscopy using 1,4-dicyanobenzene as an internal standard. ^cYield into brackets refers to chromatographically pure product. ^d40% of (*E*)-2-dodecenal was formed during the reaction.

(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 alkoxy 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.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 (sulfonamidyl, carbamidyl, 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. Pleasingly, 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-l**. It is worth noting that the late-stage functionalization of more complex molecules such as (*S*)-(-)-perrilaldehyde, (*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**, bromoacetonitrile **5c**, 2-iodo-1,1,1-trifluoroethane **5d**, 2-bromo-2-nitropropane **5e**, or 2-bromoacetophenone derivatives **5f-i** could also be selectively

Scheme 2: Scope of γ -alkoxylation, γ -amination and γ -alkylation.^a

^a General conditions: **1** (0.2 mmol), **2** (0.36 mmol) or **5** (0.30 mmol), Ir(ppy)₃ (0.004 mmol) and K₂HPO₄ or K₂CO₃ (0.4 mmol) in 2 mL of MeCN or CHCl₃ irradiated with 5W blue LEDs at rt for 18 h. Unless otherwise noted, given yields refer to chromatography pure products. ^b dr > 95:5. ^c With 0.3 mmol of **2** in 3 mL of MeCN or CHCl₃. ^d dr = 4.5:1. ^e Yield into brackets corresponds to ¹H NMR yield using 1,3-dinitrobenzene as internal standard. ^f dr = 1.1:1. ^g The dr value is assumed to be 1:1.

incorporated in γ position, leading to the corresponding enals **6p-w** in up to 81% yield.

To demonstrate the synthetic utility of this γ -regioselective process, a 4-mmol scale experiment was performed with substrate **1a** and reagent **5a**. After 18h of irradiation, 450 mg of γ -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 γ -functionalization of enals: treatment of 2-dodecenal with 2,4,6-

collidine and triisopropylsilyl triflate provided first the corresponding silylated dienol ether **1a** without any purification or isolation. This intermediate was then exposed to photocatalyzed γ -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 γ -functionalization reaction. As both light and Ir^{III} 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}(**2a**) = -0.47 V vs SCE,¹⁴ and E^{red}(**5a**) = -0.62 V vs SCE)¹⁵ 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.

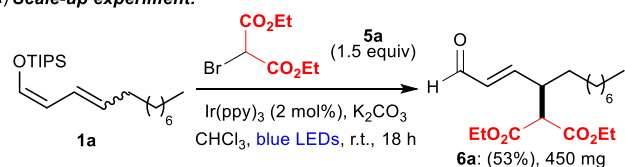
In summary, we have developed a versatile and general radical approach for the γ-functionalization of enals. Importantly, this new visible-light mediated process operates with perfect site-selectivity even in the challenging case of unbiased α-unbranched enals, and is applicable to the synthesis of a 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

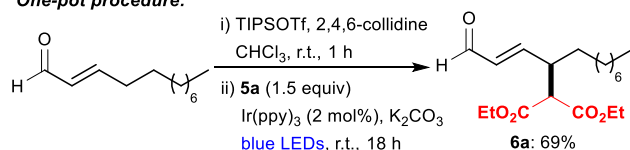
There are no conflicts to declare.

Scheme 3: (a) Synthetic utility. (b) Plausible mechanism of γ-functionalization.

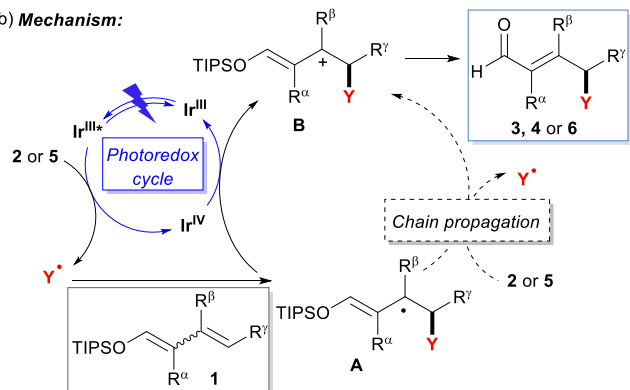
(a) **Scale-up experiment:**



One-pot procedure:



(b) **Mechanism:**



Acknowledgements

This work was supported by a grant from the Agence Nationale de la Recherche with JCJC funding (ANR-20-CE07-0008-01). Drs Elsa Anselmi and Emmanuel Magnier are acknowledged for fruitful discussions.

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