A photocatalytic regioselective direct hydroaminoalkylation of aryl-substituted alkenes with amines

Natalia A. Larionova,[b] Jun Miyatake Ondozabal,[b] Emily G. Smith,[b] Xacobe C. Cambeiro[a,b,*]

[a] School of Science, University of Greenwich. Chatham Maritime, ME4 4TB United Kingdom

[b] Department of Chemistry, School of Biological and Chemical Sciences, Queen Mary University of London. Mile End Rd, London, E1 4NS United Kingdom

x.cambeiro@gre.ac.uk

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ABSTRACT: A photocatalytic method for the α-selective hydroaminoalkylation of cinnamate esters has been developed. The reaction involves the regioselective addition of α-aminoalkyl radicals generated from aniline derivatives or aliphatic amines to the α-position of unsaturated esters. The scope of aromatic alkenes was extended to styrenes undergoing hydroaminoalkylation with anti-Markovnikov selectivity, which confirms the importance of the aromatic group at the β-position. Simple scale-up is demonstrated under continuous flow conditions, highlighting the practicality of the method.

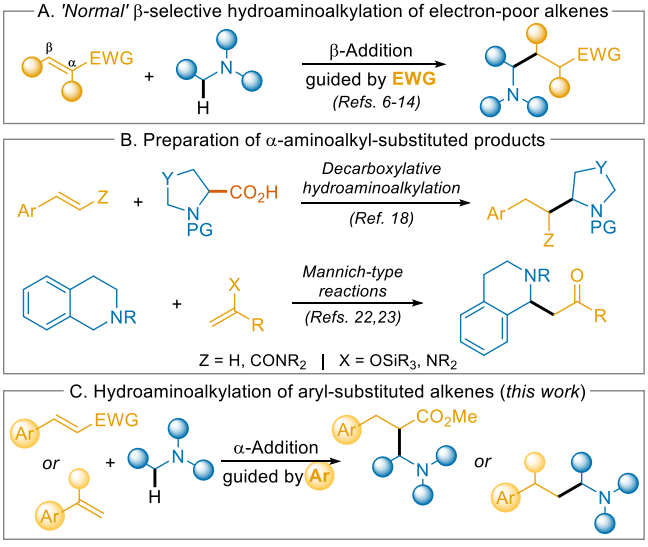
Photocatalytic hydroaminoalkylation of electron-poor alkenes has been developed throughout the last decade[1,2] taking advantage of the nucleophilic character of α-aminoalkyl radicals.[3] Thus, radicals generated by visible light photooxidation of tertiary amines[4] have been shown to engage in conjugate addition with a variety of Michael acceptors such as such as maleimides,[5] alkylidene malonates and malononitriles,[6] α,β-unsaturated carbonyl compounds,[7] amides[8] and esters,[9] as well as alkenylpyridine derivatives.[10]. In addition, photocatalytic conjugate additions[11] have been described with α-aminoalkyl radicals generated by different methods, such as oxidative desilylation[12] or decarboxylation,[13] among others.[14]

These transformations proceed generally with high regioselectivity for the β-position respect of the electron-withdrawing group (Figure 1a), consistent with an early transition state governed by the SOMO-LUMO interaction. As a remarkable exception, Sparling observed α-selectivity in a photocatalytic decarboxylative radical addition to β-aryl α,β-unsaturated amides (Figure 1b).[15] The unusual selectivity in this case was attributed to a reversible radical addition, giving place under thermodynamic control to the more stable benzylic radical. However, this method was limited to decarboxylative generation of the α-aminoalkyl radical from α-amino acid substrates, which required a strongly oxidising catalyst for decarboxylation.[16]

A method for the direct α-selective aminoalkylation of α,β-unsaturated carboxylic acid derivatives would provide a practical, straightforward route for the preparation of β-amino acids, potentially enabling access to substitution patterns (β^2 and $\beta^{2,3}$) which are not easily accessible through more established routes.[17] Alternative photocatalytic methods for the preparation of β-amino carbonyl compounds from amines have been reported, based on Mannich-type reactions of photocatalytically generated iminium ions with silyl enol ethers[18] or with enamines generated *in situ* using enamine catalysis (Figure 1b).[19] However, these methods are limited to tetrahydroisoquinoline derivatives as the amine partner. A similar strategy for α-olefination of amines is similarly restricted to tetrahydroisoquinoline and tetrahydro-β-carbolines.[20]

In contrast with the well-established Giese-type addition to electron-poor alkenes, efficient photocatalytic hydroaminoalkylation of less polarised alkenes has not been reported to date.[21] This is possibly a consequence of poor chemoselectivity in the absence of a good matching of the nucleophilic radical with an electrophilic alkene, giving place to polymerisation side-reactions.[22]

Figure 1. Summary of hydroaminoalkylation of electron-poor alkenes and related transformations.



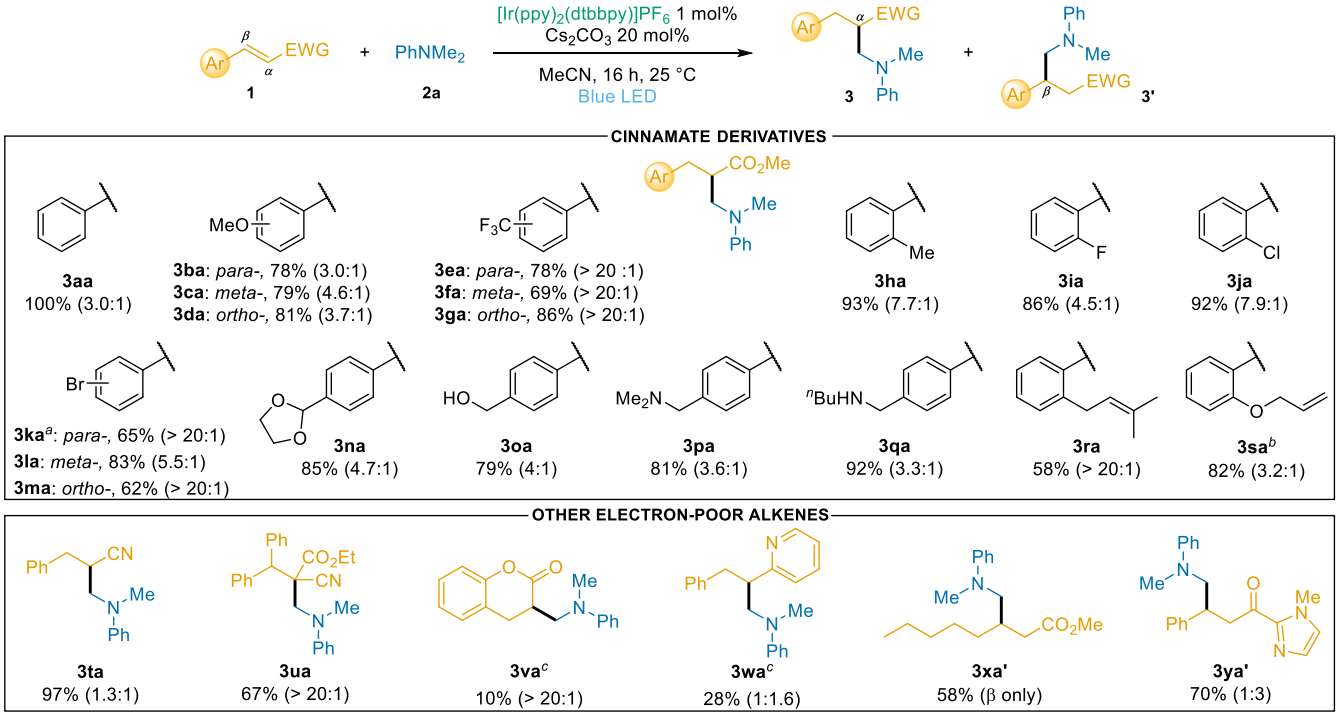
During our recent investigation on photocatalytic transfer hydrogenation of cinnamate derivatives we found a kinetic preference for attack at the α-position in a H atom transfer from Hantzsch ester radical cation to the alkene.[23] Here we report a photocatalytic method for the α-selective hydroaminoalkylation of cinnamate esters based on the regioselective addition of α-aminoalkyl radicals, where the reaction is controlled by the presence of an aromatic group at the β-position. Moreover, our method is valid for the direct hydroaminoalkylation of styrenes, which proceeds with high anti-Markovnikov selectivity (Figure 1c).

Irradiation with blue light of a MeCN solution of cinnamate ester **1a** and dimethylaniline **2a** (1.5 equiv) in the presence of photocatalyst $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%) and Cs_2CO_3 (20 mol%) resulted in quantitative formation of β-amino ester **3aa** and its γ-isomer in 3:1 ratio (Scheme 1), reflecting a preference for α-addition of the aminoalkyl radical. The use of the organic, soluble base DBU provided results comparable to Cs_2CO_3, as did the use of increased loadings of base. Other modifications to the reaction conditions resulted generally in decreased yields (see ESI 1.3 for additional details).

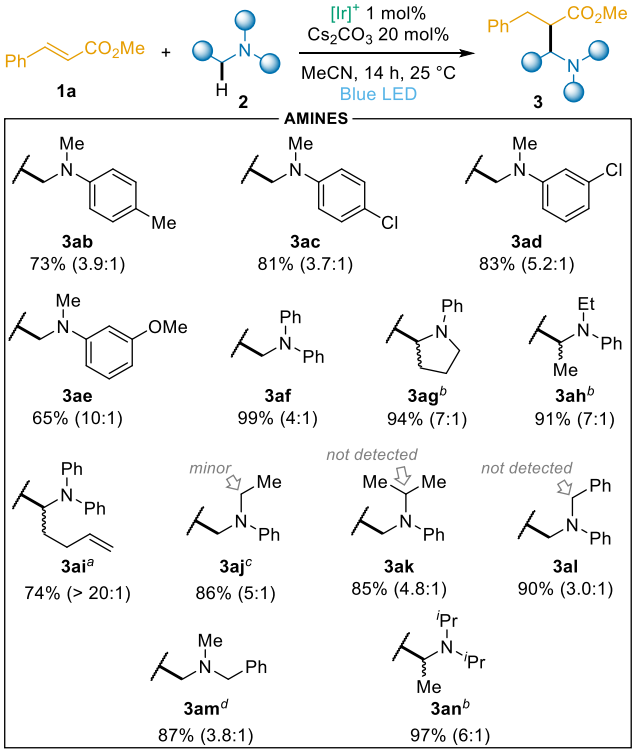
To determine the scope of the reaction we first applied it to a range of cinnamate derivatives (Scheme 1). We probed the effect of introducing an electron-donating or electron-withdrawing substituent on the different positions of the aryl ring. Namely, OMe and CF_3 were well tolerated in all cases, leading to good yields of products **3ba-da** and **3ea-ga**, respectively. Although the α-substitution product was favoured in all cases, CF_3-substituted substrates led to significantly increased regioselectivities. In both cases the position of substitution had no apparent effect on the reaction, suggesting that steric hindrance was not very relevant. Consistently, *ortho*-Me substituted product **3ha** was also readily formed. F, Cl and Br were tolerated as well and led to increased regioselectivities compared to **3aa**. These halogen substituents provide useful handles for further functionalisation of the products through metal-catalysed cross-couplings or photocatalytic transformations.[24] Similarly, the reaction was compatible with the presence of several functional groups such as acetal-protected aldehyde (**3na**), benzylic alcohol (**3oa**), tertiary (**3pa**) and even secondary amine (**3qa**). Finally, the reaction worked in the presence of a dimethylallyl or an allyloxy substituent, leading to formation of products **3ra** and **3sa** (starting from the *Z*-cinnamate) with no detectable reaction on the allyl groups. This suggests that the radical formed after addition rapidly reacts further to provide compound **3**.[25]

Cinnamonitrile was also a valid substrate for the reaction, although the corresponding product **3ta** was obtained with a very poor regioselectivity against its β-addition analogue (1.3:1). Product **3ua**, conversely, was obtained with complete regioselectivity from the corresponding tetrasubstituted alkene. A cyclic α,β-unsaturated ester, coumarin, was transformed to **3va** regioselectively albeit in very low yield (10%), and 2-styrylpyridine gave **3wa** in low yield and selectivity, with a slight preference for the β-addition product (28%, 1:1.6). Finally, an α,β-unsaturated ester bearing only an aliphatic substituent reacted to give exclusively the β-addition product **3xa'**. More electron-poor substrates such as ketones (e.g., **3ya'**), although generally compatible with the reaction, tended to give β-addition as the major product, thus we did not investigate them further.

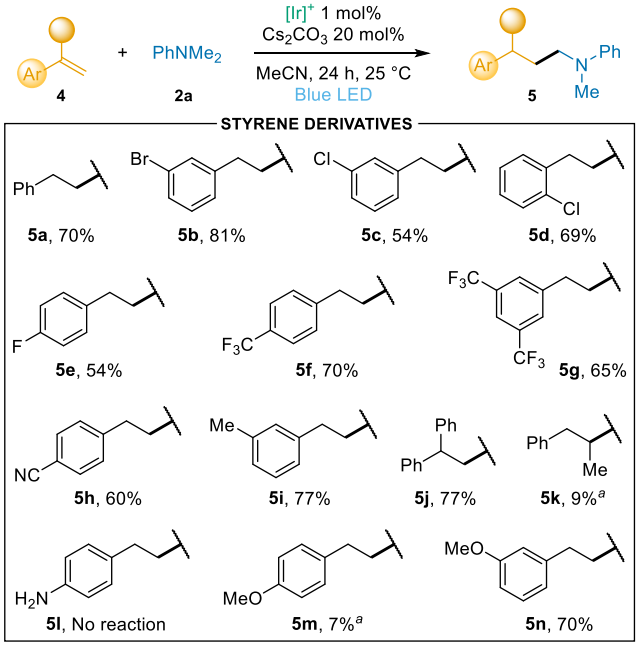
Then, we explored the reactivity of different amines (Scheme 2). The reaction proceeds well with a variety of substituted dimethylaniline derivatives (**3ab** to **3ae**) as well as with methyldiphenylamine (**3af**). *N*-phenylpyrrolidine and *N*,*N*-diethylaniline provided products **3ag** and **3ah** in excellent yields and re-



Scheme 1. Hydroaminomethylation of electron-poor alkenes (**1**) with *N*,*N*-dimethylaniline (**2a**). Reactions carried out with **1** (0.2 mmol), **2a** (1.5 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%) and Cs_2CO_3 (20 mol%) in MeCN (2 mL), under blue light irradiation for 16 h while controlling the temperature at 25 °C. Yields are of isolated product unless otherwise noted. Numbers in brackets are α to β ratio determined by ^{1}H NMR of the crude reaction mixture. [a] The ethyl ester was used in this case instead of methyl. [b] Starting material was the *Z*-alkene. [c] Yield determined by ^{1}H NMR using an internal standard.



Scheme 2. Hydroaminomethylation of methyl cinnamate (**1a**) with amines (**2**). Reaction conditions as in Scheme 1. $[Ir]^+ = [Ir(ppy)_2(dtbbpy)]PF_6$. [a] 0.2 mmol of **2** and 3 equiv. of **1a** were used. [b] Product was obtained as a mixture of diastereoisomers (see ESI). [c] Product was obtained as a 7:1 mixture of regioisomers. [d] Characterised as mixture of α/β.

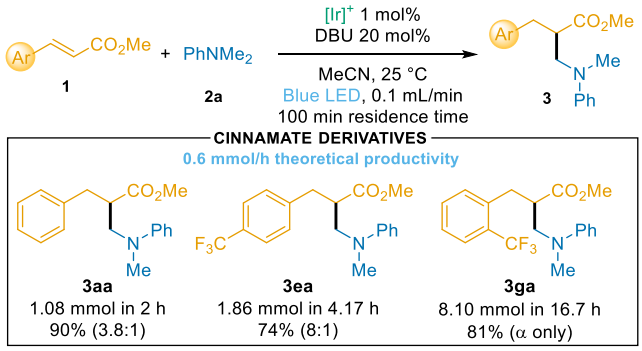


Scheme 3. Hydroaminomethylation of styrene derivatives (**4**) with *N*,*N*-dimethylaniline (**2a**). Reactions carried out with **4** (0.2 mmol), **2a** (2 equiv), $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%) and Cs_2CO_3 (20 mol%) in MeCN (8 mL), under blue light irradiation for 24 h while controlling the temperature at 25 °C. Yields are of isolated product. $[Ir]^+ = [Ir(ppy)_2(dtbbpy)]PF_6$. [a] Yield determined by ^1H NMR using an internal standard.

gioselectivities, although with poor diastereoselectivity. Similar to above mentioned observations for products **3ra** and **3sa**, an alkene-substituted diphenylamine derivative resulted in formation of product **3ai** with no cyclisation of the pendant terminal alkene. Non-symmetrically substituted anilines tended to react at the position leading to the least stable radical. Thus, *N*-ethyl-*N*-methylaniline gave **3aj** as the major product, while *N*-methyl-*N*-isopropylaniline and *N*-methyl-*N*-benzylaniline gave **3ak** and **3al**, with no reaction observed at the isopropyl and benzyl substituents, respectively. Remarkably, the reaction was not limited to aniline derivatives: products **3am** and **3an** were readily obtained from their parent amines in good yields and selectivities. This opens a way for the application of the present reaction to more diverse and useful products, however further optimisation is still needed to extend the scope to diverse aliphatic amines.[26]

Finally, we explored the reactivity under our conditions of styrene derivatives, not bearing the electron-withdrawing group on the alkene (Scheme 3). Both styrene and a range of substituted derivatives reacted smoothly with *N*,*N*-dimethylaniline to give the corresponding hydroaminomethylation products **5a-i** in good yields (54 to 81%) and with complete anti-Markovnikov regioselectivity.[27] Similarly, 1,1-diphenylethene provided product **5j** in 77% yield. β-Methylstyrene reacted with the same selectivity but providing a very poor yield of **5k**. It is worth noting that, while these examples show that an electron-withdrawing group directly bound to the alkene was not necessary, high electron density was still detrimental to the reaction: Thus, *p*-aminostyrene did not react and *p*-methoxystyrene provided only low yields of the product (**5l**, **5m**). A *m*-methoxy substituent, having an overall electron-withdrawing effect (Hammet σ_m = +0.115 *vs.* σ_p = −0.268), provided **5n** in 70% yield.

The simple conditions employed allowed for the straightforward translation into a readily scalable continuous flow method. Thus, a MeCN solution of alkene, amine and catalyst containing 20 mol% of DBU was pumped through a coil of PTFE tube which was irradiated with blue LEDs. The collected solution, after workup and purification, afforded the corresponding β-amino ester product. This method was applied, with excellent results, to the preparation of compounds **3aa**, **3ae** and **3ag** (Scheme 4).



Scheme 4. Continuous-flow production of β-amino esters.

A plausible mechanism for the reaction (Figure 2) would involve reductive quenching of the excited catalyst ($E° Ir/*Ir^+ = 0.76$ V) by amine **2** ($E° 2^+/2 = 0.71$ V) followed by deprotonation to form and aminoalkyl radical **B**,[28,29] which would then add across the alkene substrate (**1** or **4**) double bond. Reduction of the resulting benzylic radical $\mathbf{C}_\alpha$ followed by protonation would lead to product **3** or **5**. Control experiments

supported the formation of the α-aminoalkyl radical under our reaction conditions, promoted by the presence of Cs_2CO_3 (Figure S3, ESI). Also, deuteration at the benzylic position was observed when the reaction was performed in the presence of D_2O (Figure S4).

Figure 2. Plausible mechanism for the hydroaminoalkylation.

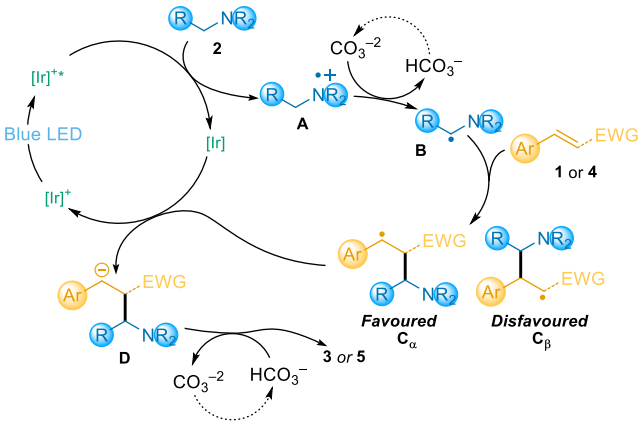
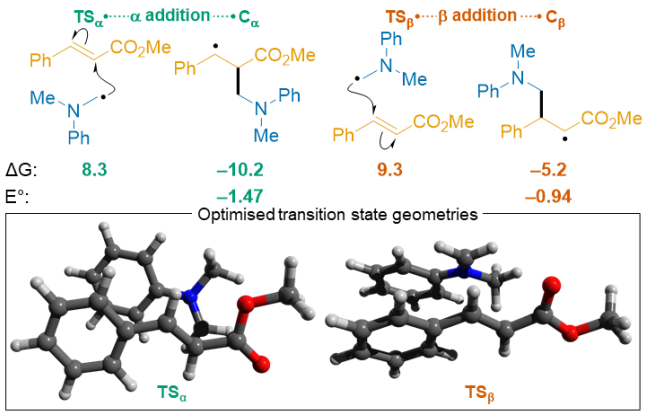


Figure 3. DFT-calculated energy profile for the radical addition [PBE0-GD3/6-31+G(d,p), ΔG: Gibbs free energies in solution (SMD model for MeCN) relative to sum of separate reagents reported in kcal/mol]. E°: Calculated reduction potentials *vs.* SCE reported in V.



DFT calculations (PBE0-GD3/6-31+G(d,p), SMD model for MeCN, Figure 3) were consistent with our mechanistic hypothesis: Transition states for the radical addition at positions α and β were both energetically accessible, with addition at α favoured by 1.0 kcal/mol, a small but significant difference consistent with the observed regioselectivity. Furthermore, the radical addition step was exergonic by −10.2 and −5.2 kcal/mol, respectively, for the α and β additions, and the calculated reduction potentials of the resulting benzylic or enol radical (−1.47 and −0.94 V) indicate an easy reduction to the corresponding anions by the reduced form of the catalyst (E^0 = −1.51 V vs. SCE).[28a] These observations, combined with the absence of cyclisation products in the reactions leading to compounds **3ra**, **3sa** and **3ai**, provide support for a kinetic control of regioselectivity rather than a reversible radical addition under thermodynamic control. It is likely that this observation may extend to other radical additions to moderately electron-poor alkenes.

In conclusion, the methodology presented allows the hydroaminoalkylation of a wide variety of moderately electron-poor alkenes, including styrene derivatives, with aniline derivatives as well as aliphatic amines. Besides, the method is readily scalable under continuous flow conditions. Computational data suggest that the reaction is driven by the presence of the aromatic substituent, which controls reactivity and regioselectivity. An accurate balance between the aromatic substituent and the electron-withdrawing group are necessary for selectivity, with stronger EWGs leading to Giese-type addition, which will be of importance for the development of related regioselective methodologies further expanding the scope of these transformations.

ASSOCIATED CONTENT

Supporting Information. Further details on reaction optimisation, characterisation of all new compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* x.cambeiro@gre.ac.uk

Author Contributions

The manuscript was written through contributions of all authors.

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23. Larionova, N. A.; Miyatake Ondozabal, J.; Cambeiro, X. C., Reduction of Electron-Deficient Alkenes Enabled by a Photoinduced Hydrogen Atom Transfer. *Adv. Synth. Catal.* **2021**, *363* (2), 558-564.

24. Iodine-substituted substrates provided complex mixtures with only low yield of the hydroaminoalkylation product.

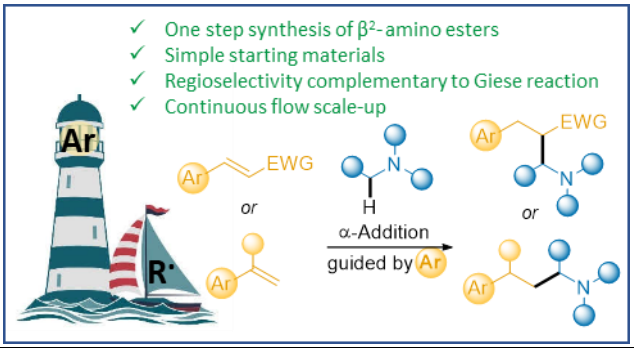
25. Newcomb, M. Radical Kinetics and Clocks. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; John Wiley & Sons, Ltd, 2012.

26. For example, *N*-methylpyrrolidine and *N*-methylpiperidine both reacted with good conversions to give mixtures of regio- and diastereomeric hydroaminoalkylation products.

27. The only detected by-products were double alkylation of the amine with two units of the alkene, and a dehydrogenated derivative of product **5**.

28. This process is well-precedented, see for example: Prier, C. K.; MacMillan, D. W. C. Amine α-Heteroarylation via Photoredox Catalysis: A Homolytic Aromatic Substitution Pathway. *Chem. Sci.* **2014**, *5* (11), 4173–4178.

29. (a) Wu, Y.; Kim, D.; Teets, T. S., Photophysical Properties and Redox Potentials of Photosensitizers for Organic Photoredox Transformations. *Synlett* **2021**. https://doi.org/10.1055/a-1390-9065. (b) Fukuzumi, S.; Yuasa, J.; Satoh, N.; Suenobu, T. Scandium Ion-Promoted Photoinduced Electron Transfer from Electron Donors to Acridine and Pyrene. Essential Role of Scandium Ion in Photocatalytic Oxygenation of Hexamethylbenzene. *J. Am. Chem. Soc.* **2004**, *126* (24), 7585–7594.


✓ One step synthesis of β²-amino esters
✓ Simple starting materials
✓ Regioselectivity complementary to Giese reaction
✓ Continuous flow scale-up
Ar
R•
Ar
EWG
or
Ar
N
H
α-Addition
guided by Ar
Ar
EWG
N
or
Ar
N