Synthesis of Alcohols: Streamlined C1 to Cn Hydroxyalkylation through Photoredox Catalysis

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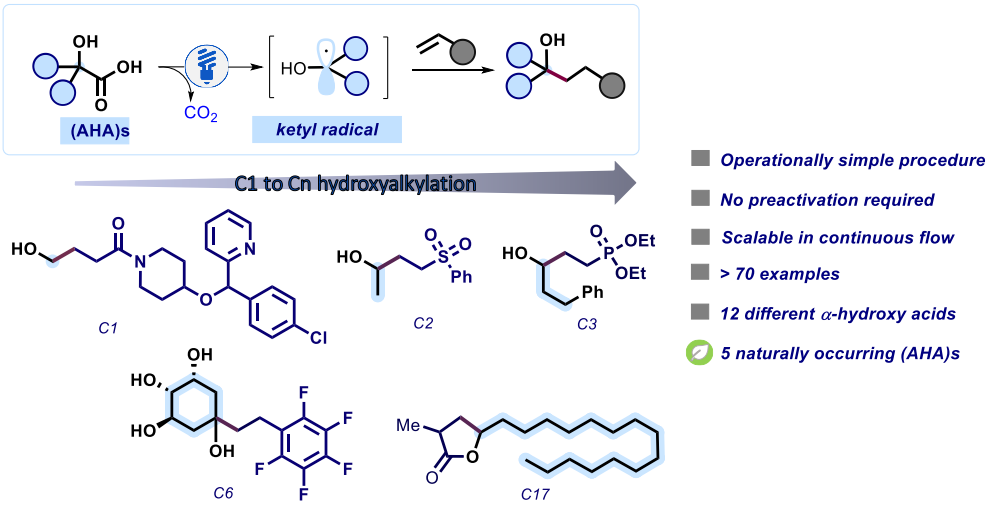


Naturally occurring and readily available α-hydroxy carboxylic acids (AHAs) are utilized as platform for visible light-mediated oxidative CO_2-extrusion furnishing α-hydroxy radicals proved to be versatile C1 to Cn hydroxyalkylating agents. The decarboxylative direct Giese reaction (DDGR) is operationally simple, not requiring activator or sacrificial oxidants and enabled the synthesis of a diverse range of hydroxylated products, introducing a connectivity typically precluded from conventional polar domains. Notably, the methodology has been extended to widely used glycolic acid resulting in a highly efficient and unprecedented C1 hydroxyhomologation tactic. The use of flow technology further facilitates the scalability and adds green credentials to this synthetic methodology.

Introduction

The introduction of a single hydroxyl group in a molecular structure can dramatically influence the drug–receptor binding affinity through the creation of an extensive hydrogen bond network.[1] Approximately 37% of marketed drugs contain at least one hydroxyl group in their structure (Fig. 1A). Moreover, the -OH group can serve as a handle for further derivatizations. Within the polar domain, direct β-hydroxyalkylations could be achieved through two different synthetic pathways. In a less explored approach introduced by Tamao, α-silyl carbanions are employed as α-hydroxyalkyl anion equivalents in a formal nucleophilic α-hydroxyalkylation reactions (Fig. 1, B, path a).[2] Moreover, this strategy represents an indirect hydroxyalkylation approach that requires the oxidative cleavage of the carbon-silicon bond at the end of the synthetic sequence. More commonly, hydroxyalkyations are generally achieved through the addition of organolithiums or Grignard reagents to carbonyl compounds (Fig. 1, B, path b), and recently the limited

functional groups tolerance of these highly reactive reagents has been overcome through the use of flow microreactor technology.[3] Neverthless, the direct one-step preparation of γ-hydroxy substituted derivatives is retrosynthetically precluded from the polar mechanisms due to a polarity mismatch (Fig. 1, B, path c). In this context, the renaissance of radical chemistry showcased that approaches to C–C bond formation, divorced from polar approaches, can offer novel pathways for accessing valuable structures in a more direct manner.[4,5,6] With regard to radical hydroxyalkylations, Leonori reported an hydroxymethylation strategy based on the addition to formaldehyde of alkyl radicals generated by halogen-atom transfer (XAT) from the corresponding iodides (Fig. 1, C, path a).[7] This approach requires the photochemical generation of an α-aminoalkyl radical that promotes the halogen-atom transfer, and an excess of PPh_3 as trapping agent of the transient O-radical. Interestingly, open-shell chemistry also provides a mechanistically inverted strategy for hydroxyalkylations based on the coupling between ketyl radicals and unsaturated acceptors.[8,9] In fact, ketyl radicals or ketyl radical anions, characterized by a nucleophilic carbon radical, provide a mechanism for reversing the reactivity of the initial carbonyl compound. This enables their utilization in alternative C–C bond-forming reactions with non-nucleophilic partners. These versatile open-shell species are usually generated from aldehydes or ketones through single electron transfer (SET) reduction, with strong reductants (e.g., Na, K, Ti) to overcome the large reduction potential of carbonyls. In this context, Kagan's reagent (SmI_2) stands out as one of the most frequently employed reagents.[10] In recent years, the advent of photoredox catalysis has led to the application of novel photochemical approaches in addressing this thermodynamic challenge as shown by Knowles, Yoon, Rueping, Cozzi, and others.[11,12,13,14,15,16] However, these methodologies require a synergistic Lewis acid/photoredox catalysis and/or the use of Hantzsch ester as a sacrificial electron and hydrogen atom donor. Interestingly, an electro-photocatalytic carbonyl reduction has been recently proposed by Wickens and coworkers (Fig. 1, C, path b).[17] Furthermore, Nagib presented a redox-neutral generation of ketyl radicals through *in situ* conversion of aldehydes to α-acetoxy iodides followed by Mn-catalyzed atom transfer under visible light irradiation.[8] A complementary method for accessing α-hydroxy radicals involves the C–H abstraction from alcohols through visible light-promoted hydrogen atom transfer (HAT) (Fig. 1, C, path c).[18,19,20] These methodologies require a combination of photoredox and HAT catalysis in the presence of other phosphorous- or boron-based activators capable to overwhelm the bond dissociation energy (BDE) of α-hydroxy Csp^3–H bonds.

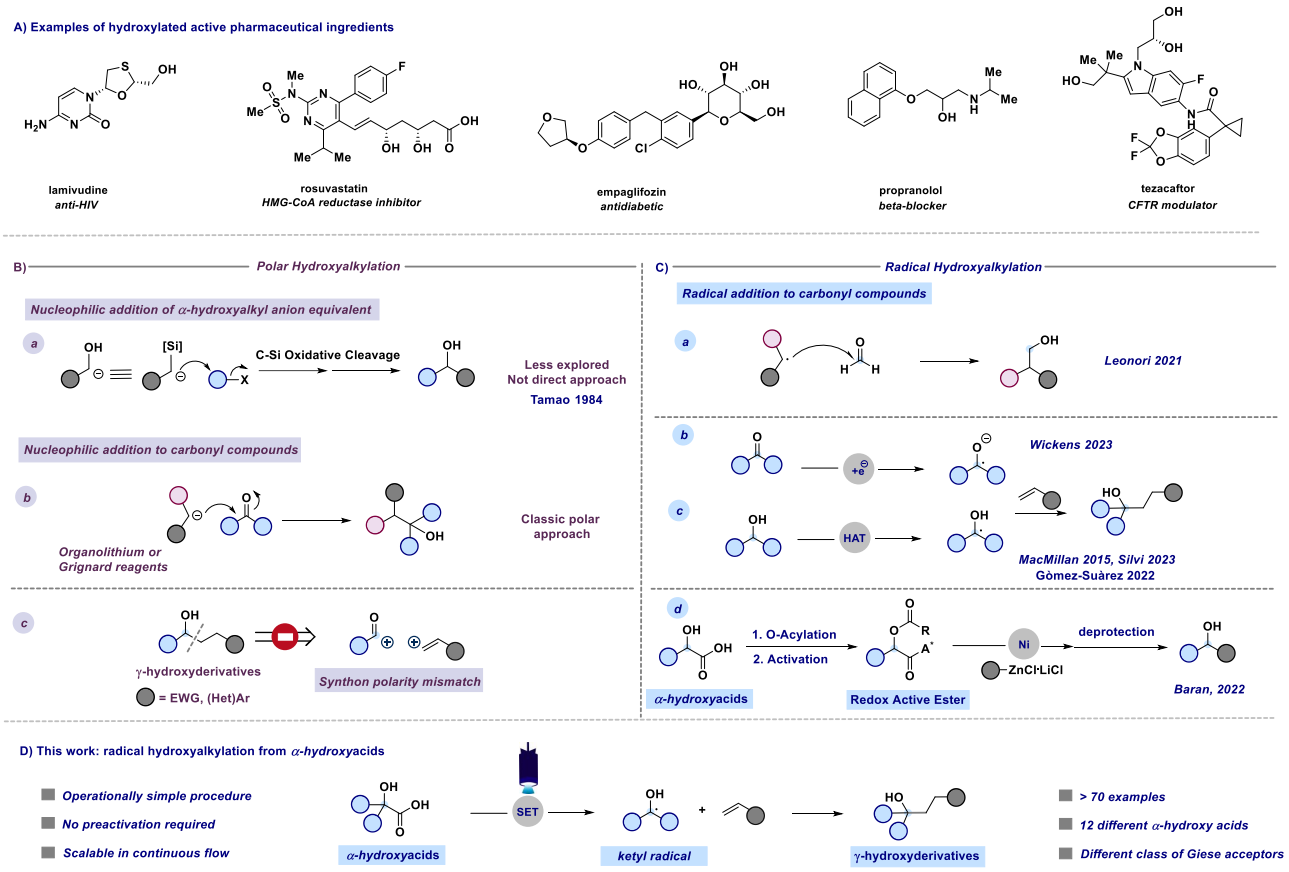


Fig. 1. A) Examples of therapeutic agents containing hydroxyalkyl motifs. Overview of the main approaches for incorporating a hydroxyalkyl motif in both polar (B) and radical (C) domains. D) This work unlocks the utilisation of α-hydroxy acids as synthetic platform for radical hydroxyalkylations.

Despite extensive research in the chemistry of α-hydroxyalkyl radicals, we contemplate whether a more direct approach to accessing these versatile intermediates was feasible using readily available starting materials. In other words, we aimed to circumvent the need for complex synergistic catalytic systems or activators, aligning to achieve a more sustainable and easily accessible route to valuable molecules. Recently, Baran reported a radical-based approach for the enantioselective decarboxylative Negishi coupling to obtain enantiopure dialkyl carbinols. The methodology relies on the conversion of α-hydroxy acids into redox-active esters (RAEs) using a one-pot O-protection and acid activation protocol (Fig. 1, C, path d).[21] Inspired by Baran's work and aimed at developing sustainable processes using readily available feedstocks we found α-hydroxy acids as readily available linchpins for radical hydroxyalkylations.[22] Indeed, α-hydroxy acids (AHAs) constitute a group of naturally occurring organic carboxylic acids, finding applications in various fields such as medicine, food processing, cosmetics, polymer synthesis, water treatment, and more.[23]

Glycolic acid (GA) stands as the simplest alpha hydroxy acid (AHA) and is naturally occurring.[24,25] Lactic acid (LA), found in sour milk and tomato juice, holds the "*Generally Recognized As Safe (GRAS)*" status, endorsed as harmless by the United States Food and Drug Administration with a growing global demand.[26,27,28] In this context, we questioned whether it would have been possible to leverage AHAs as naturally occurring and readily available reactants to deliver α-hydroxy radicals under visible light irradiation using a green and operationally simple procedure. We report herein a comprehensive study on the generation and use of hydroxyalkyl radicals via decarboxylative direct Giese reaction (DDGR).

Result and discussion

A previous attempt to use α-hydroxyacids as ketyl radical precursors was documented by Gonzalez-Gomez and coworkers in 2016. The authors reported a transition-metal-free method for the decarboxylative

generation of radicals from carboxylic acids and subsequent coupling with Giese-type acceptors under visible-light irradiation.[29] However, in this investigation, the oxidative decarboxylation of lactic acid (2-hydroxypropanoic acid) using 9-mesitylene-10-methylacridinium perchlorate ([Acr-Mes]ClO_4) and Na_2CO_3, respectively as photocatalyst and base, was reported to be unsuccessful. Despite the disappointing results documented in this study and, to the best of our knowledge, the lack of effective methods for generating hydroxyalkyl radicals from the corresponding hydroxy acids, we maintained confidence in the potential to develop an efficient hydroxyalkylation strategy in order to fill this gap. We started our study using 2-hydroxy-3-phenylpropanoic acid **1a** and methyl acrylate as model substrates. Being the generation of ketyl radicals from α-hydroxy acids unprecedented, we performed cyclic voltammetry investigations and computational studies to evaluate the feasibility of the synthetic plan shown in Fig. 2. Initial cyclic voltammetry (CV) assessment suggested that 2-hydroxy-3-phenylpropanoic acid **1a** cannot be readily oxidized ($E_{1/2}$ = +2.13 V vs SCE). Conversely, the corresponding carboxylate **1a**$^-$ exhibited an oxidation potential ($E_{1/2}^{red}$ = +1.04 V vs SCE) that aligns well with the redox window of various organic and metalloorganic photocatalysts.[30] From a sustainable standpoint, we looked at an inexpensive and transition-metal-free organic photocatalyst such as 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN).[31] As outlined in Fig. 2, we envisioned an initial excitation of the photocatalyst 4CzIPN (**A**) to 4CzIPN* (**A***) under visible light, followed by a reductive quenching of the excited 4CzIPN* (**A***) ($E_{1/2}^{A^*/A^{\cdot-}}$ = +1.35 V versus SCE in CH_3CN) and consequent oxidation of the carboxylate **1**$^-$ triggering the extrusion of CO_2, and formation of the desired α-hydroxy radical **2** and 4CzIPN$^{\cdot-}$ (**A**$^{\cdot-}$). Addition of the nucleophilic α-hydroxy radical **2** to methyl acrylate would furnish alkyl radical **3**. Single-electron reduction of this electron-deficient radical **3** operated by 4CzIPN$^{\cdot-}$ (**A**$^{\cdot-}$) ($E_{1/2}^{A/A^{\cdot-}}$ = -1.21 V versus SCE in CH_3CN) would then furnish the α-hydroxy alkylated product **4** after protonation regenerating the photocatalyst 4CzIPN (**A**). To gain insight into the reactivity of α-hydroxyalkyl radicals and the feasibility of the proposed catalytic cycle, we conducted a preliminary computational study of the Giese addition reaction utilizing radical **2a** as the model substrate computationally coupled to three different Giese acceptors in DMSO as the solvent (Fig. 2, B). Initially, calculations were performed at the SMD(DMSO)-ωB97X-D3/def2-TZVP//ωB97X-D3/def2-SVP level of theory (at 298.15 K, 1 M).[32,33,34,35] The results indicated that the addition reaction of radical **2a** to methyl acrylate is moderately exergonic ($\Delta G°$ = -18.4 kcal mol^{-1}) with a relatively low energy barrier ($\Delta G^{\ddagger}$ = 10.3 kcal mol^{-1}), making it highly feasible at room temperature (Fig. 2, B). The calculation of reduction potentials performed at the SMD(DMSO)-M06-2X/ma-def2-TZVP//ωB97X-D3/def2-SVP level finally suggested that the reaction of **2a** with methyl acrylate through the designed catalytic cycle is very likely to occur.[36] In fact, the Giese adduct **3a** arising from the attack of **2a** to methyl acrylate holds a calculated reduction potential of -0.76 V versus SCE. Therefore, the single electron transfer process operated by 4CzIPN$^{\cdot-}$ ($E_{1/2}^{A/A^{\cdot-}}$ = -1.21 V versus SCE) is expected to be thermodynamically favoured corresponding to a cell potential of +0.45 V (ΔG^0 = -10.4 kcal mol^{-1}, see Supporting Information). In striking contrast, the calculated reduction potential of **2a** of -1.93 V versus SCE allowed us to exclude the occurrence of the direct reduction of **2a** operated by 4CzIPN$^{\cdot-}$ which is thermodynamically disfavoured corresponding to a cell potential of -0.72 V (ΔG^0 = +16.6 kcal mol^{-1}).

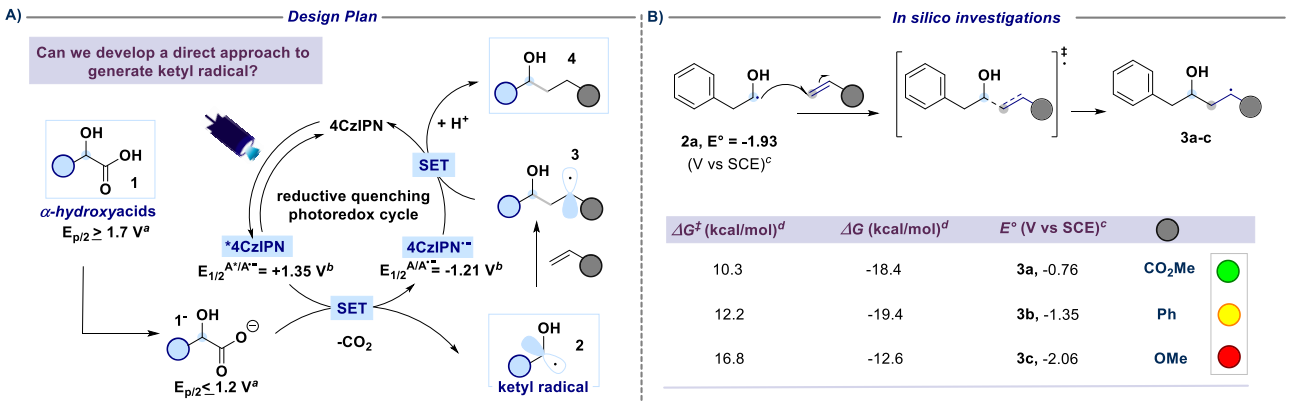


Fig. 2 Reaction development. A) Design plan for the direct generation of ketyl radical from α-hydroxy acids. SET, single-electron transfer**.** [a]Oxidation potentials measured by cyclic voltammetry in a 0.1 M solution of NBu_4PF_6 in MeCN at 25 °C with 100 mV s^{-1} scan rate and reported vs SCE. Carboxylates generated *in situ* through the addition of a solution of NBu_4OH. Here, the potentials at half the peak ($E_{p/2}$) are reported. See the Supporting Information for further experimental details. [b]Literature values vs SCE in MeCN.[37] B) Computational studies on the addition of the ketyl radicals to unsaturated acceptors. [c]Values calculated at the SMD(DMSO)-M06-2X/ma-def2-TZVP//ωB97X-D3/def2-SVP level of theory (298.15 K, 1 M) [d]Values calculated at the SMD(DMSO)-ωB97X-D3/def2-TZVP//ωB97X-D3/def2-SVP level of theory (298.15 K, 1 M).

Additionally, the reaction of **2a** with other SOMOphiles such as styrene and methyl vinyl ether was also investigated *in silico*, and such reactions were similarly found to be exergonic ($\Delta G°$ = -19.4 and -12.6 kcal mol^{-1} respectively) but with slightly higher activation barriers ($\Delta G^{\ddagger}$ = 12.2 and 16.8 kcal mol^{-1} respectively). However, the calculated reduction potential of the Giese adducts **3c** (-2.06 V versus SCE) was found to mismatch the potential required for the closure of the catalytic cycle, suggesting that such electron-rich substrates might prove ineffective in performing the desired coupling reaction. Differently, the calculated reduction potential for adduct **3b** (-1.35 V versus SCE) is only slightly different from the one of $4CzIPN^{\cdot-}$ implying that the effectiveness of such SOMOphile in partecipating in the catalytic reaction could not be completely ruled out. The nucleophilic character of the ketyl radicals reported in this study was proved by calculating the global electrophilicity index ω whose value was < 1 eV (see supporting information for details).[38,39] Delighted by these computational results, and bearing in mind that hydroxylakylations were predicted to be successful on electron-poor acceptors, we began the optimization campaign by subjecting 2-hydroxy-3-phenylpropanoic acid **1a** and methyl acrylate to blue light irradiation in the presence of 4CzIPN (2.5 mol%), 2,6-lutidine, and using dimethyl sulfoxide as reaction solvent. Disappointingly, the expected α-hydroxy alkylated product **4a** was observed only in traces (Fig. 3). Similarly, the use of DABCO furnished very low yield of **4a**, while switching to the inorganic bases Na_2HPO_4 to promote the formation of the corresponding carboxylate $\mathbf{1a}^-$ returned **4a** in 22% yield. An excellent result was observed using K_3PO_4 which provided **4a** in 90% yield (Fig. 3, chart 1). Similar results were observed with the use of potassium tert-butoxide (88% yield). A substoichiometric amount of base was detrimental for the yield. Particular attention was given to the reaction time. Indeed, extending the duration from 2 to 3 hours led to a significant increase in yield, achieving complete conversion of the starting reagents (Fig. 3, chart 5). Interestingly, when the duration was extended to 16 hours, intramolecular lactonization of **4a** occurred, leading to the complete formation of lactone **5**. Consequently, the developed transformation could result in two distinct products by merely adjusting the reaction time. The preliminary optimization study used a concentration of 0.31 M in DMSO that could be increased up to 0.77 M without compromising the efficiency of the reaction (Fig. 3, chart 4). Furthermore, increasing the light source power from 40 to 128 W did not adversely affect the reaction performance (refer to Fig. 3, chart 6). A solvent screening revealed that polar aprotic solvents, such as dimethylformamide (DMF) or dimethyl sulfoxide, yielded superior results, whereas the use of acetonitrile, 2-methyltetrahydrofuran, and dichloromethane hindered the reaction (see Fig. 3, chart 3). However, DMSO was chosen as preferred solvent for this process because, comparatively, it offers a less hazardous alternative to DMF.[40] Evaluation of alternative photocatalysts commonly employed for decarboxylation reactions (see Fig. 3, chart 2) established 4CzIPN as the most effective catalyst.

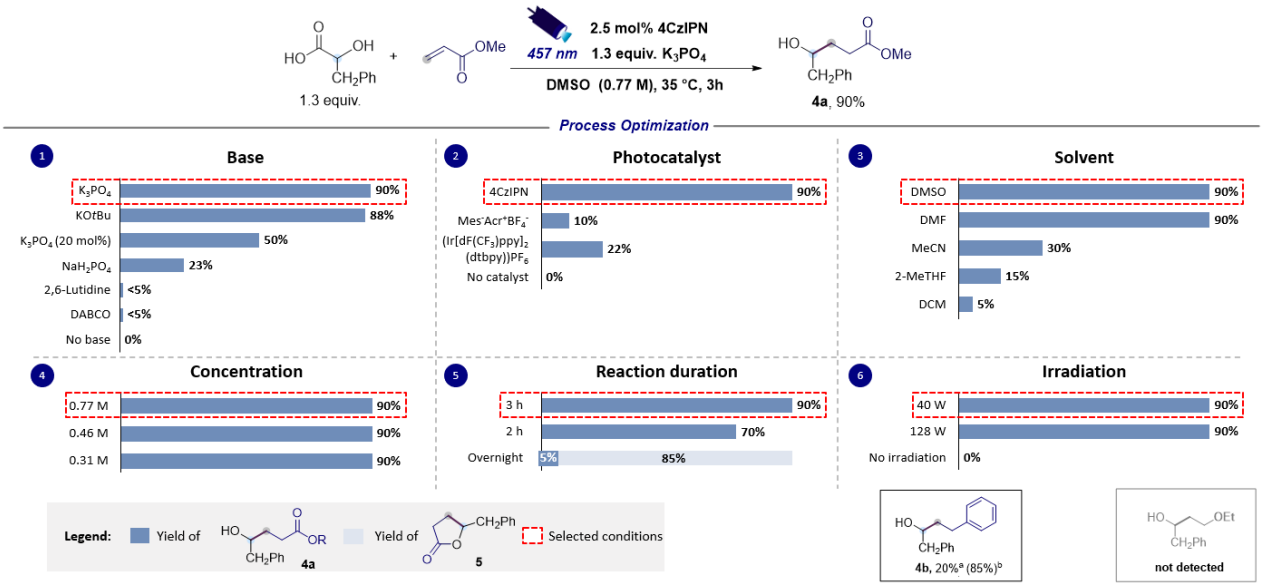


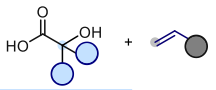
Fig. 3 Optimization of radical hydroxyalkylation involving ketyl radicals. Yields were determined by proton NMR spectroscopy using dibromomethane as an internal standard. [a]Reaction performed using 40 W and a reaction time of 16 hours. [b]Reaction performed using 128 W and a reaction time of 16 hours. Abbreviations: Me, methyl; Ph, phenyl; equiv., equivalents; DABCO, 1,4 Diazabicyclo[2.2.2]octane; 4CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; ppy, 2-phenylpyridyl; dtbbpy, 4,4'-di-tert-butyl-2,2'- bipyridyl; DMSO, dimethyl sulfoxide, DMF, N,N´-dimethylformamide; 2-MeTHF, 2-Methyltetrahydrofuran; DCM, dichloromethane; M, molarity; h, hours; W, watt.

Under the optimized conditions, electron rich SOMOphile such as vinylethyl ether and styrene were tested as reaction partners in the radical hydroxyalkylation. With our delight, and according to the computational results (Fig. 2), hydroxyalkylation occurred only with styrene leading to **4b** while no reaction was observed with vinylethyl ether. This result further supports the nucleophilic nature of the ketyl radical **2a**. Subsequently, armed with the optimal conditions, we explored the range of α-hydroxy carboxylic acids suitable for this radical addition protocol. Aiming to establish a robust and broadly applicable synthetic method, we tested 12 different α-hydroxy carboxylic acids (**1a-l**). Additionally, cyclic voltammetry measurements were conducted on each of the 12 distinct α-hydroxy acids (refer to Supporting Information) to confirm their compatibility with the synthetic approach outlined in Fig. 2. As reported in Fig. 4, a range of structurally diverse α-hydroxy acids (**1a-j**) underwent efficient coupling with readily available acrylates furnishing products **4a, 6-23** in good to excellent yields (70-95%). Moreover, this decarboxylative protocol can be also applied to the addition of tertiary α-hydroxy radicals to acrylates leading to products **19-23** in excellent yields (77-95%). Not surprisingly, a competing lactonization was observed with α-substituted acrylates after 3 hours of reaction time. However, prolonging the reaction duration to 16 hours provide lactone derivatives **10**, **11**, **18** and **23** as exclusive products and in very good yields (70-93%). Next, varied Giese-type acceptors were evaluated in the radical hydroxyalkylation reaction. As reported in Fig. 5, optimized conditions could be successfully applied to acrylamides acceptors furnishing interesting and hardly to make γ-hydroxylated amides **24-28** in good to excellent yields (70-95%). Remarkably, the unprotected indole core was fully compatible with the optimized protocol (Fig. 4, compound **27**). Notably, also electron-poor alkenes, such as 4-chlorostyrene and 2-vinylpyridine could be adopted as coupling partners of ketyl radicals producing the corresponding hydroxyalkylated derivatives **29-33** in moderate to excellent yields (51-90%).

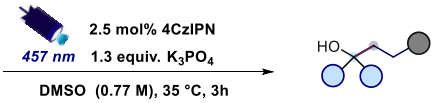
Radical Hydroxyalkylation[a]

Alpha hydroxy acids (AHAs) as a platform for the generation of ketyl radicals

Acid, $E_{p/2} > +1.7$ V vs SCE[b]
Carboxylate, $E_{p/2} \leq +1.2$ V vs SCE[b]



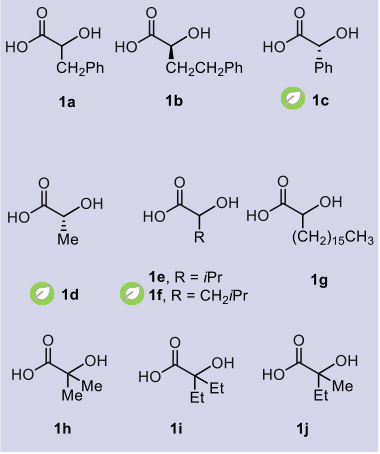
11 different AHAs



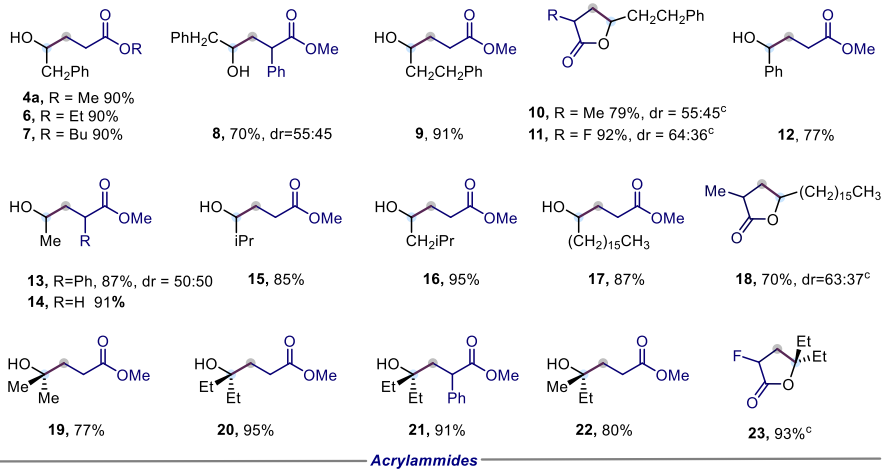
43 examples

via 

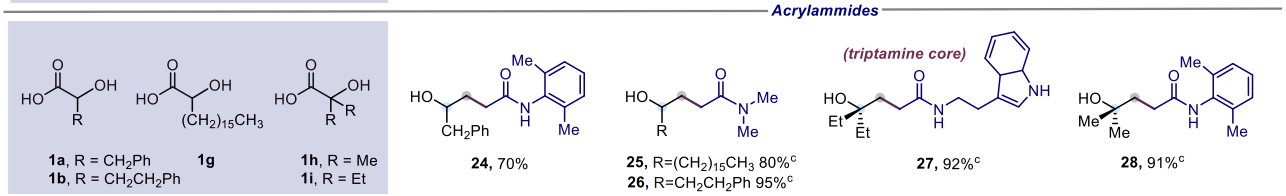
HAAs



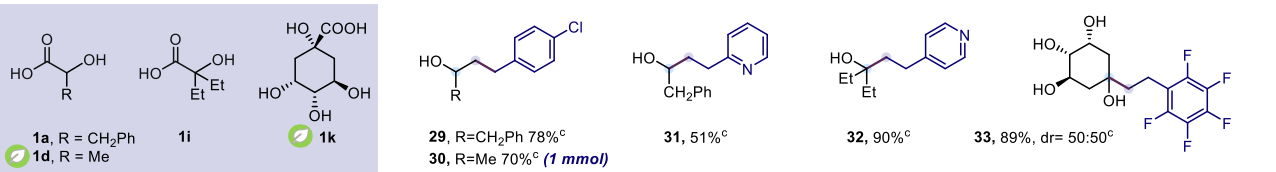
Acrylates



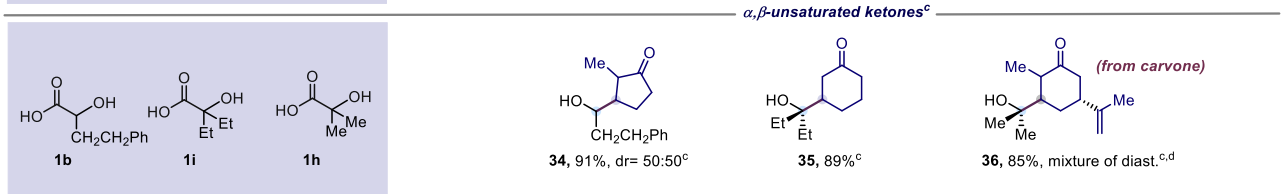
Acrylammides



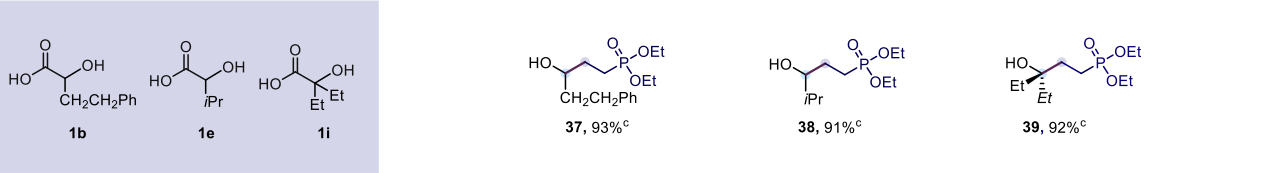
Alkenes[c]



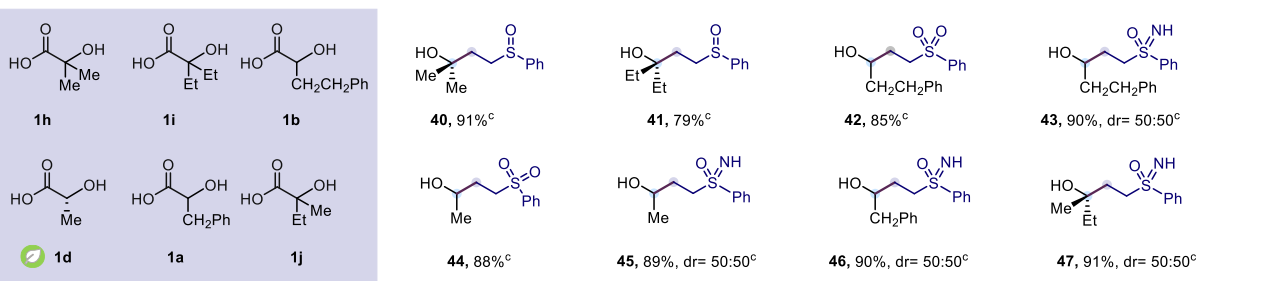
α,β-unsaturated ketones[c]



Phosphorus-containing SOMOphiles[c]



Sulfur-containing SOMOphiles[c]



= *naturally occurring (AHA)s*

Fig. 4. Scope for radical hydroxyalkylation from AHAs. [a]Reaction performed using optimized reaction conditions: unsaturated acceptor (0.23 mmol, 1 equiv.), α-hydroxy acid (1.3 equiv.), K_3PO_4 (1.3 equiv.), and 4CzIPN (2.5 mol%) in DMSO (0.77 M) as solvent. The mixture was irradiated with 457 nm light (40 W) for 3 h unless otherwise specified. Isolated yields are reported. [b]Oxidation potentials measured by cyclic voltammetry. Refer to the Supporting Information for further details. [c]A reaction time of 16 hours was used instead of 3 hours. [d]Reaction performed using 128W instead of 40W. Abbreviations: Ph, phenyl; Me, methyl; *i*Pr, isopropyl; Et, ethyl.

Notably, the synthesis of hydroxylated adduct **30** can be scaled up to 1 mmol without compromising reaction efficiency. α,β-Unsaturated ketones including carvone were found as competent SOMOphiles for this transformation leading to products **34-36** (89-91%). The radical hydroxyalkylation could be executed on heterosubstituted Giese-type acceptors. We were pleased to find that γ-hydroxy phosphonates **37-39** could be prepared in excellent yields (91-93%) through the addition of α-hydroxy radicals to diethyl vinylphosphonate (Fig. 4).[41] Moreover, the optimized mild reaction conditions are compatible with the use of several sulfur-containing Giese-type acceptors, including vinyl sulfoxides (product **40**, **41**, 79-91%), sulfoximines (products **43**, **45-47**, 89-91%), and sulfones (products **42**, **44**, 85-88%). Remarkably, the study of the scope of the reaction was extended to naturally occurring AHAs such as lactic acid (**1d**), mandelic acid (**1c**) and quinic acid (**1k**). To our delight, lactic acid smoothly reacted with acrylates giving the corresponding adducts **13-14** in excellent yields (87-91%). Similarly, mandelic acid reacted with methyl acrylate furnishing product **12** in 77% yield (Fig. 4). Remarkably, the cyclic polyol quinic acid, readily obtainable from coffee beans and other natural sources,[42] was found to be effective in the radical hydroxylation of pentafluoro styrene producing the corresponding adduct **33** in 89% yield (Fig. 4). However, the protocol proved ineffective for certain Giese acceptors (See Supporting Information for further details).

Encouraged by these findings and the broad applicability of the methodology, we pondered whether it would be feasible to achieve a more challenging and unprecedented C1 hydroxyalkylation using the readily available glycolic acid (GA). Indeed, GA stands out as the simplest alpha hydroxy acid and occurs naturally in plants such as sugarcane, pineapple, and sugar beets. While chemical synthesis continues to be the primary method for GA production, considerable efforts are being made to establish sustainable GA production processes. This positions GA as an economical and easily accessible chemical with significantly lower toxicity compared to an alternative radical C1 synthon, such as methanol.[43] In order to fulfil our curiosity and introduce a new and elegant method for hydroxymethylation of organic scaffolds, we subjected GA (**1j**) and methyl acrylate to blue light irradiation under optimized reaction conditions. This preliminary test was executed utilizing d_6-DMSO as the solvent for a direct NMR analysis of the reaction crude and to mitigate issues associated with the volatility and water solubility of the expected product **48**. Astonishingly, ^{1}H NMR of the reaction crude revealed the almost quantitative formation of the desired hydroxymethylated product **48** (Fig. 5). Excited by this result, we next sought to assess the generality of this new radical C1 hydroxyhomologation strategy testing various unsaturated acceptors. According to the previously reported α-hydroxy acids, high yields were obtained in the C1-hyroxyhomologation using acrylates (products **49-56**, 55-95% in Fig. 5). Remarkable chemoselectivity was observed in the presence of additional unsaturations, exemplified by the use of allyl acrylate furnishing **54** in 85% yield. Moreover, the C1-hyroxyhomologation of a menthol derivative led to **55** in 95% yield, while an azetidine-containing acrylate provided **56** in 93% yield. This hydroxy methyl radical could be also successfully coupled with N-aryl acrylamides resulting in compounds **57** and **58** formed in 55 and 70%, respectively. Notably, this approach facilitates the introduction of the hydroxymethyl fragment onto a derivative of the bioactive amantadine (product **59**, 93% yield) and enables the efficient preparation of derivative **60**, which contains the structural core of the antihistaminic bepotastine, in 91% yield. Lastly, the C1-hyroxyhomologation with sulfur-containing SOMOphiles was tested. Specifically, we succeeded in the hydroxymethylation of two vinylic sulfones giving products **61** and **62** in 50 and 93% respectively, and a vinylic sulfoximine forming **63** in 38% yield.

Next, the C1-hyroxyhomologation of electron-deficient alkenes was evaluated (Fig. 5). Vinyl pyridines smoothly reacts with the putative hydroxymethyl radical giving the corresponding adducts **64** and **65** in high

yields (80 and 85% respectively). Similarly, the reaction with styrenes bearing electron withdrawing substituents produced **66** and **67** in 87% and 80% yield respectively. Interestingly, the use of α-(trifluoromethyl)styrene returned gem-difluoroalkene **68** in 85% yield. Formation of **68** could be explained considering the catalytic cycle described in Fig. 2, where reduction of radical **3** is followed by a fluoride anion elimination which likely occurs faster than protonation (*vide infra*).[44] Furthermore, hydroxymethyl radical could be coupled with α,β-unsaturated ketones, including carvone and a naproxene derivative, producing compounds **69**-**72** in good to excellent yields (60-95%). However, during the investigation of the scope of the reaction we embarked in ineffective SOMOphiles (Fig. 5).

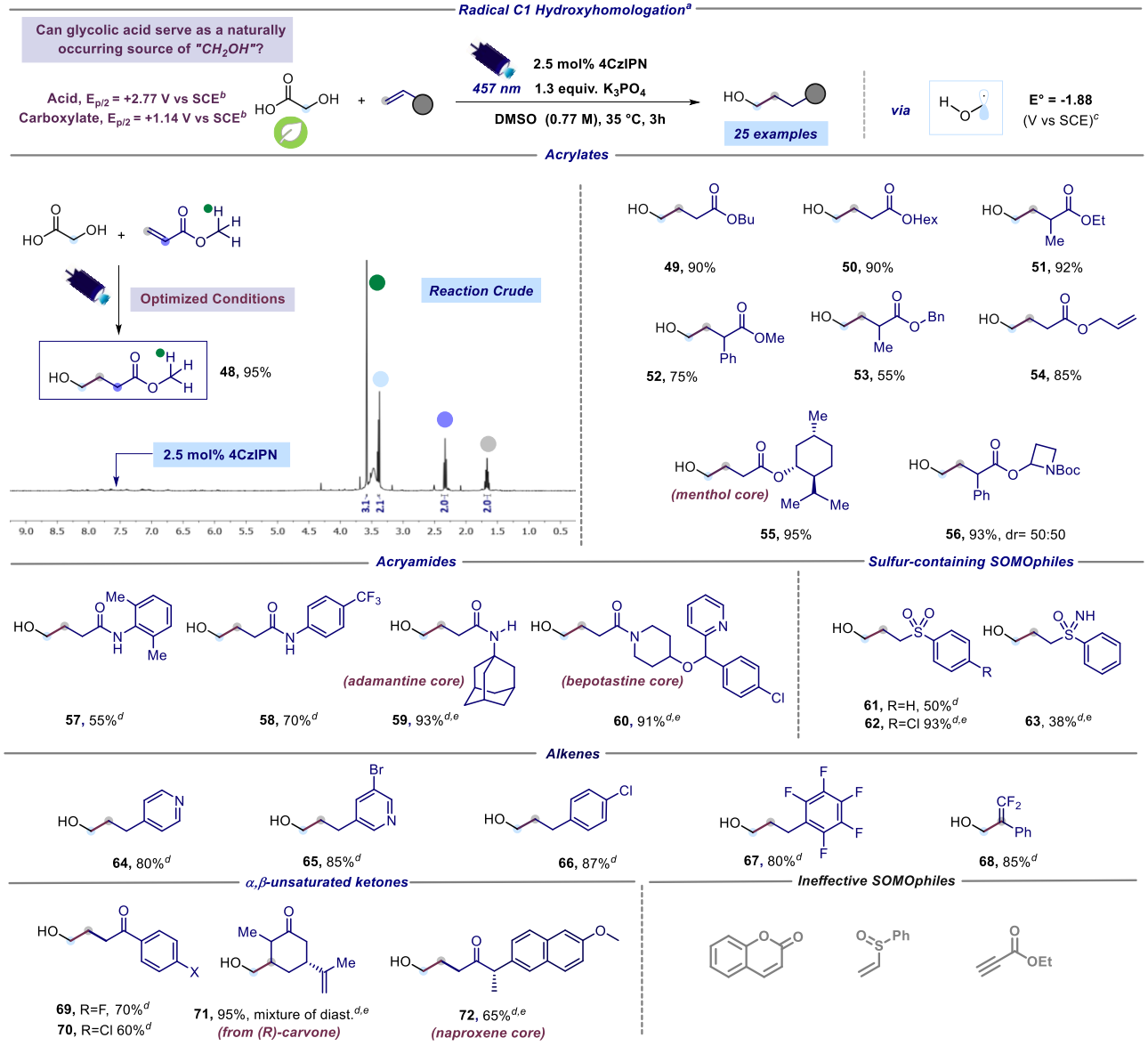


Fig. 5. Scope of the radical hydroxymethylation protocol. [a]Reaction performed using optimized reaction conditions: unsaturated acceptor (0.23 mmol, 1 equiv.), glycolic acid (1.3 equiv.), K_3PO_4 (1.3 equiv.), and 4CzIPN (2.5 mol%) in DMSO (0.4 M) as solvent. The mixture was irradiated with 457 nm light (40 W) for 3 h unless otherwise specified. Isolated yields are reported. [b]Oxidation potentials measured by cyclic voltammetry. Refer to the Supporting Information for further details. [c]Values calculated at the SMD(DMSO)-M06-2X/ma-def2-TZVP//ωB97X-D3/def2-SVP level of theory (298.15 K, 1 M). [d]A reaction time of 16 hours was used instead of 3 hours. [e]Reaction performed using 128W instead of 40W. Abbreviations: Me, methyl; Et, ethyl; Bu, butyl; Hex, hexyl; Bn, benzyl; Ph, phenyl; Tf, triflyl.

Mindful of the inherent challenges posed by batch photocatalytic methods at scale, our subsequent objective was to transition this hydroxyalkylation reaction to a continuous-flow platform.[45,46,47] Based on our expertise

in microfluidic technology,[48,49,50] we identified some issue in the batch protocol that would hinder transitioning to a flow process. Firstly, the heterogeneous nature of the reaction mixture would result in non-uniform irradiation and limited light penetration when operating at larger scales. Consequently, we replaced K_3PO_4 with potassium tert-butoxide (KO*t*Bu) to handle a homogeneous reaction mixture. Secondly, the light power needed to be increased to 128 W to achieve a more efficient irradiation. Adopting these adjustments, we set out to explore the feasibility of the radical hydroxyalkylation in continuous flow focusing on naturally occurring AHAs such as glycolic, lactic, and mandelic acids (Fig. 6). We were pleased to find that the continuous flow protocol not only yielded similar or higher yields compared to batch processing but also allowed for a significant reduction in reaction time (See Supporting Information for further examples under continuous flow conditions). It is worth pointing out that the benzylic radical, generated from mandelic acid (**1c**), which was thought to be unreactive under photoredox conditions,[51] was effectively employed using our SET protocol. Pleasingly, the continuous flow platform facilitates the efficient production of **30** at 5 mmol scale and in high yields. Furthermore, the assessment of productivity and STY (space time yield) for the preparation of **30** in flow (204 mg·h^{-1} and 25,4 g·L^{-1}h^{-1}, respectively) and batch (1,9 mg·h^{-1} and 1,7 g·L^{-1}h^{-1}, respectively) clearly demonstrated the advantage of the flow protocol compared to batch.

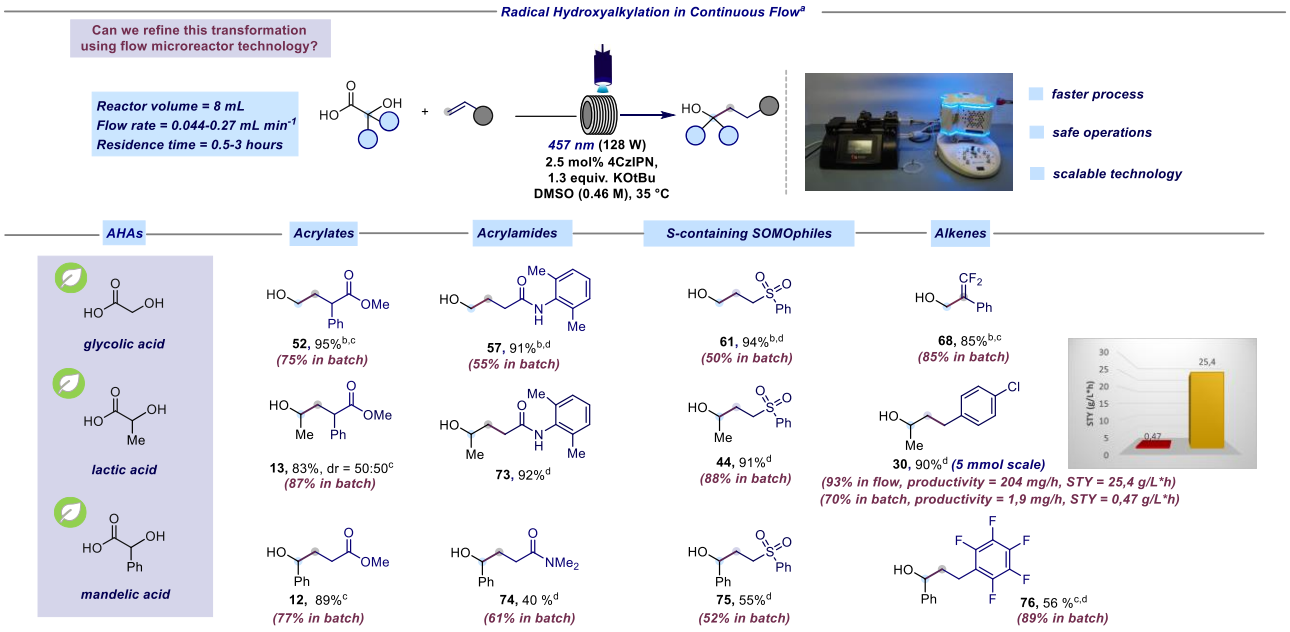


Fig 6. Radical hydroxyalkylation in continuous flow. [a]Reaction performed using optimized reaction conditions: unsaturated acceptor (0.23 mmol, 1 equiv.), α-hydroxy acid (1.3 equiv.), KO*t*Bu (1.3 equiv.), and 4CzIPN (2.5 mol%) in DMSO (0.46 M) as solvent. The mixture was irradiated with 457 nm light (40 W) using a residence time of 0.5 hours unless otherwise specified. Isolated yields are reported**.** [b]The reaction was performed by premixing the hydroxy acid and the base before adding the photocatalyst (see Supporting Information for further details). A concentration of 0.08 M was used. [c]Reaction performed using 40W instead of 128W. [d]A residence time of 3 hours was used.

After assessing the synthetic versatility of this C1 to Cn radical hydroxyalkylation, a mechanistic investigation was undertaken with the aim to further support the synthetic design proposed in Fig. 2. The addition of radical inhibitors like TEMPO (2,2,6,6-Tetramethyl-1-piperidinyloxy) or BHT (butylated hydroxytoluene) resulted in complete inhibition of the reaction (Fig. 7, A). Moreover, on-off experiments revealed that no conversion occurred in the dark, and the reaction resumed in the presence of light, showcasing the requirement for continuous light irradiation to achieve complete conversion of the reactants (Fig. 7, B).[52] Additionally, Stern−Volmer quenching studies reveal that the carboxylate of the alpha-hydroxy acid is capable to quench the excited state of the photocatalyst (4CzIPN*). On the other hand, we did not observe any luminescence decrease of 4CzIPN* in the presence of the unsaturated SOMOphile. These observations

collectively support the mechanistic proposal that the excited state 4CzIPN* behaves as the oxidant of α-hydroxy acids in the photoredox catalytic cycle (see Fig. 2).

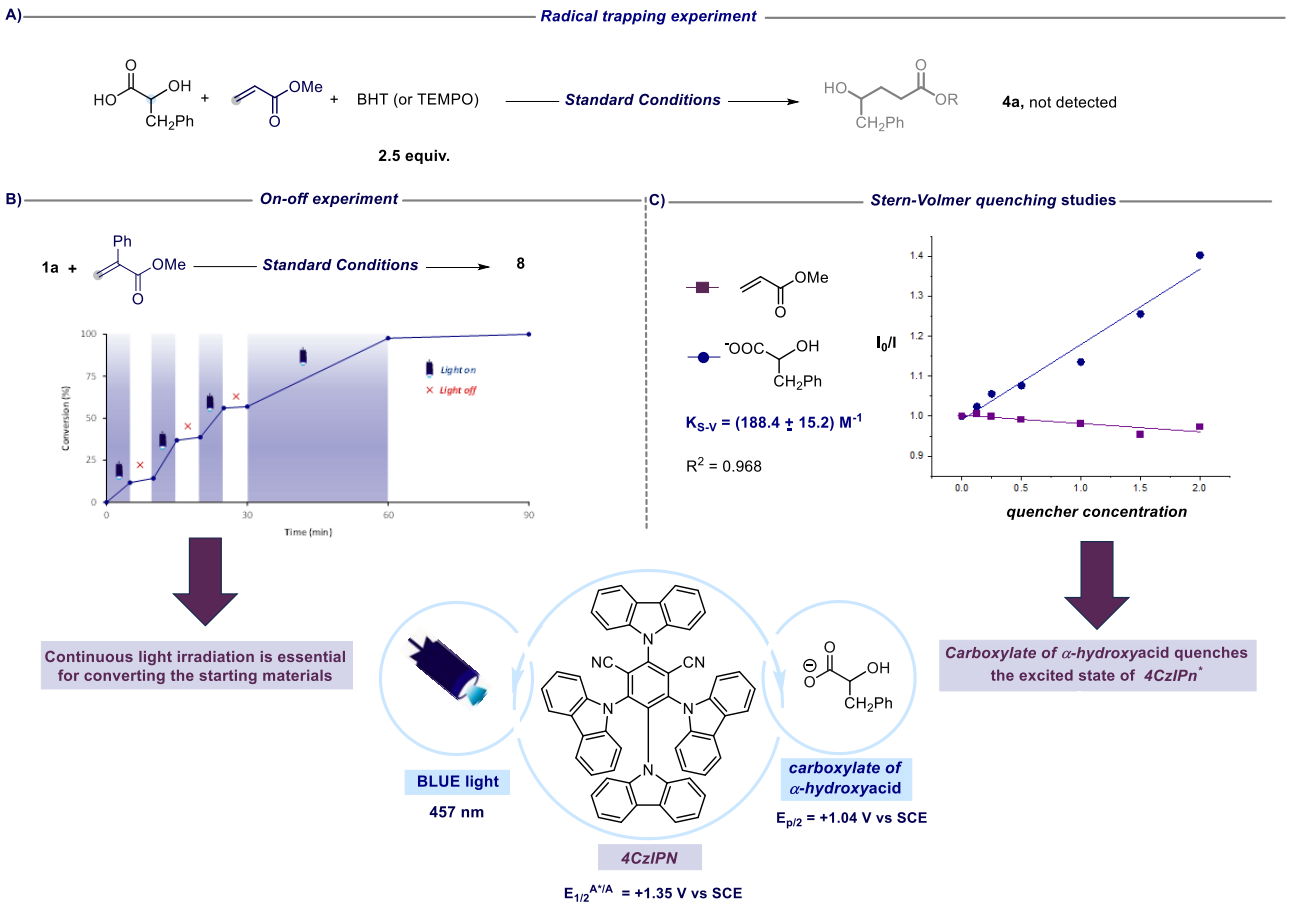


Fig. 7. Mechanistic Investigation. A) Radical trapping experiment using 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) or (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO). B) Light on-off cycles. C) Stern–Volmer quenching studies of the *4CzIPN excited state by carboxylate of acid **1a** and methyl acrylate.

In essence, we have pioneered a straightforward photoredox γ-hydroxyalkylation method by seamlessly coupling α-hydroxyalkyl radicals with unsaturated Giese-type acceptors. This operationally user-friendly technique reveals a wide generality, exhibiting a broad applicability to both α-hydroxy carboxylic acids (AHAs) and Giese-type acceptors. Furthermore, it facilitates late-stage functionalization of biorelevant structures. Of particular significance is the utilization of naturally occurring AHAs, including widely available glycolic and lactic acids, as precursors for generating corresponding C1 and C2 α-hydroxy radicals. Notably, the flow protocol has outperformed conventional batch procedures, underscoring the remarkable capabilities of flow microreactor technology in intensifying and scaling up photochemical processes. This pioneering disclosure represents a rare demonstration on the use of abundant α-hydroxy carboxylic acids (AHAs) as a platform for direct generation of versatile ketyl radicals. We anticipate that this direct methodology will not only offer operational simplicity but also contribute to improved sustainability and broaden the applicability in the synthetic utilization of α-hydroxy radicals.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information.

Author contributions

M.C. and R.L. conceived and designed the project. F.P. and Y.G. performed most of the experiments. M.A.

performed computational investigations. G.R. performed CV and Stern-Volmer experiments. All authors contributed to the writing and editing of the manuscript.

Competing interests

The authors declare no competing financial interest.

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