Visible-Light-Assisted the Metal-Free 1,2-Carboimination of Alkenes to Synthesize Complex 1,6-Amino Alcohols

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Abstract: Herein, we report a visible-light-mediated synthesis of highly complex 1,6-amino alcohols through the 1,2-carboimination of alkenes leading by an energy transfer (EnT) mechanism. This protocol successfully achieved the simultaneous formation of C(sp^3)–C(sp^3) and C(sp^3)–N bonds after several cascade steps: homolysis of the O-N bond, carbon dioxide and acetonitrile extrusion, 1,5-hydrogen atom transfer (HAT), Giese-type and radical additions. This additive and metal-free method presented a broad functional tolerance, and its value was proved with the late-stage installation of the 1,6-amino alcohol motif in biomolecules and pharmaceuticals. Finally, the versatility of the 1,6-iminyl alcohols products is showcased through their conversion to a variety of useful intermediates applicable to target-directed synthesis.

Introduction

Nitrogen functional group is present in several active compounds, being of great importance the development of simple strategies to insert this functionality. Numerous approaches have been disclosed to achieve this goal, highlighting the carboamination of double bonds.[1] Alkenes are highly versatile and readily accessible building blocks that lend themselves to the flexible assembly of densely functionalized molecules with significant structural complexity and diversity. Thus, the direct 1,2-carboamination of olefins has emerged as one of the most attractive and practical approaches within the alkene difunctionalization framework, for the subsequent formation of C–C and C–N bonds.[2]

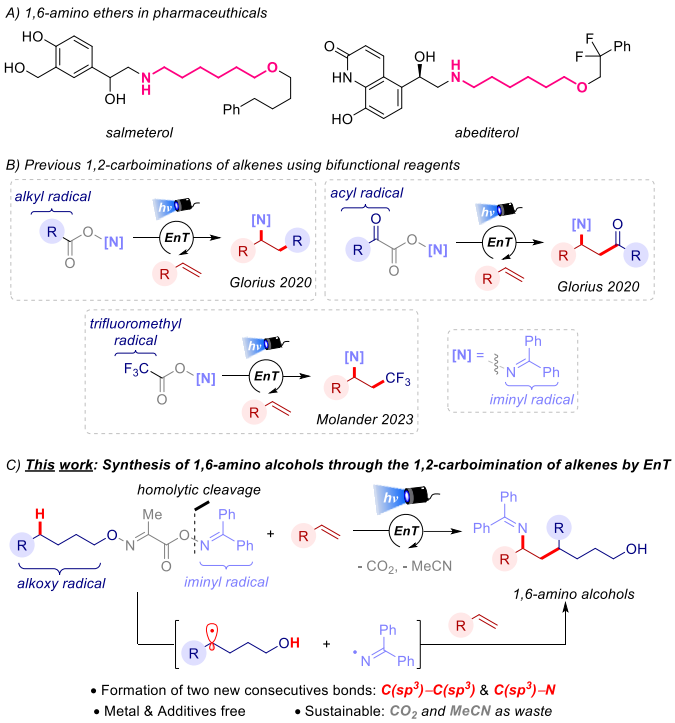


Figure 1. A) 1,6-amino ethers in biologically active compounds. B) Previous 1,2-carboimination reactions by EnT mechanism. C) General synthesis of complex 1,6-amino alcohols through the 1,2-carboimination of alkenes.

The emerge of visible-light-mediated reactions overcame the harsh conditions typically showed by traditional transformations. Specifically, non-photochemical 1,2-carboaminations required the use of transition metal catalysts and/or high temperatures. Photochemical 1,2-carboamination strategies engaged a radical-polar crossover (RPC),[3] a ligand-to-metal charge-transfer (LMCT) with elaborate copper complexes,[4] or an energy transfer (EnT) mechanism,[5-8] allowing the introduction of complexity under mild conditions. However, all the RPC 1,2-carboaminations still used precious transition metal photocatalysts, and were based on the match of the redox potential between the photocatalyst and the involved species. Contrary, the majority of the EnT protocols employed an organophotocatalyst and a bifunctional reagent, which transferred both the transient C-centered and the persistent iminyl radicals to an alkene in a one-pot process. In 2020, the group of Glorius related the use of oxime esters of alkyl carboxylic acids to accomplish an intermolecular 1,2-carboimination of activated alkenes (Figure 1B, left).[5a] The same group also described an intermolecular aminocarboxylation for the synthesis of β-amino acids by the use of bifunctional oxime oxalate ester (Figure 1B, center).[6a] Later, Molander's group discovered a vicinal imino-trifluoromethylation of alkenes using oxime esters of trifluoroacetic acid (Figure 1B, right).[8a] Additionally, two different catalyst-free three-component 1,2-carboamination of alkenes via visible-light activation was recently published. While Studer *et al.* reported the addition of an amidyl radical to vinyl boronic esters,[9] the group of Ritter developed a trifluromethylation/amination of alkyl 2-arylacrylates via α-carbonyl activation.[10] However, although a lot efforts have been dedicated to discover new 1,2-carboamination reactions, the synthesis of 1,6-amino alcohols using this strategy remains still unexplored.

1,6-amino alcohols are versatile synthetic building blocks in organic chemistry, embedded in the backbone of salmeterol[11] and abediterol,[12] pharmaceuticals to treat pulmonary diseases (Figure 1A), and other highly elaborated structures such as ALC-0315, described in the formulation of Pfizer's coronavirus vaccine.[13] Even the synthetic relevance of the 1,6-amino alcohol motif, only few methods slightly described the synthesis of the simplest *N*-substituted 6-aminohexan-1-ol. Typically, these protocols involved the hydrogenation of caprolactams with hydrogen and a ruthenium catalyst,[14] the mechanochemical reduction of 6-azidohexan-1-ol with hydrazine,[15] or the reduction of 6-aminohexanoic acid with stoichiometric amounts of sodium borohydride.[16] These methods are often limited in scope, requiring harsh conditions, prolonged reaction times, and specific reagents, which restrict their broader applicability. Therefore, the direct formation of highly substituted 1,6-amino alcohols remains underexplored.

Recently, we described the synthesis of a new bifunctional reagent and their used in the synthesis of δ-amino alcohols via energy transfer (EnT) photocatalysis (Figure 1B).[17] This protocol allowed us to quickly obtain 1,4-imino alcohols from prefunctionalized alcohols without additives, generating carbon dioxide and acetonitrile as the only waste. Moreover, the group of Xu reported the use of a similar bifunctional reagent to perform a 1,2-diamination of alkenes.[18]

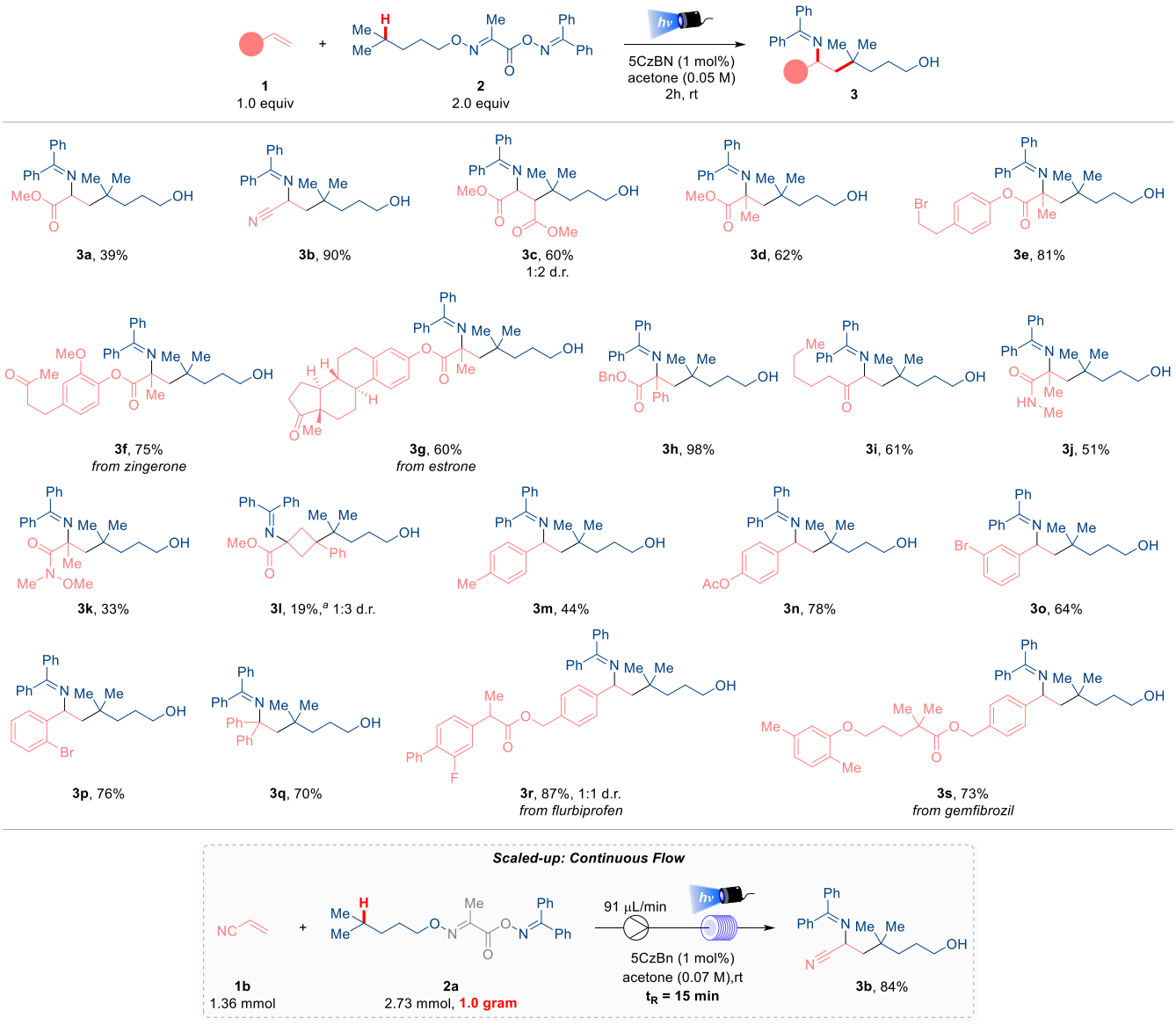
In an attempt to fulfil the gap literature, and taking into account our previous work,[17] we envisioned that complex 1,6-amino alcohols skeleton will be synthesized in a one-pot procedure using alkenes and our bifunctional reagents through an 1,2-carboimination reaction (Figure 1C). The irradiation of the bifunctional reagent in the presence of a photocatalyst will trigger the σ-homolytic cleavage of the N-O, followed by the extrusion of carbon dioxide and acetonitrile, and subsequent 1,5-hydrogen atom transfer (HAT) event to form the transient C(sp^3) radical and persistent iminyl radical intermediates. Later on, both radicals will be trapped by an alkene, elongating the carbon chain between the alcohol and the imino groups to afford the desired 1,6-amino alcohols. This method will involve the formation of two new bonds, C(sp^3)–C(sp^3) and C(sp^3)–N, in a one-step process.

Results and Discussion

Methyl acrylate (**1a**) and the bifunctional reagent **2a** were used as model substrates to study the feasibility of the proposed idea, and to optimized the reaction conditions. The best results were obtained using 2.0 equiv of **2a** and 1 mol% of the organophotocatalyst 5CzBN in acetone (0.05 M), after 2 hours of irradiation (blue Kessil lamp, λ_{max} = 427 nm), forming the expected 1,6-imino alcohol **2a** in 39% yield. Moreover, control experiments revealed that both the light irradiation and the photocatalyst are essential tools in this transformation (see supporting information for further information).

With the optimal conditions in hand, different radical acceptors and bifunctional reagents were explored (Scheme 1 and 2). Thus, various substituted alkenes were tested in presence of the bifunctional reagent **2a**, generating the desired 1,6-imino alcohols in excellent to moderate yields (Scheme 1). Non- (**1a-b**), α- (**1d-h**) and β-substituted (**1c**) acrylate-type alkenes were amenable to this protocol, showcasing that sterically effects did not affect to the reactivity, contrary to the radical stability. The stabilization of the C(sp^3)-radical intermediates induced an increase in the yield of the final product, observing the higher yield in the formation of **3h**, derived from a very stabilized benzylic, tertiary, α-carbonyl C(sp^3)-radical. Additionally, bromo handle was retained in the formation of **3e**, an important functional group for the further diversification. Other activated alkenes (vinyl ketone or vinyl amide) were suitable, affording the corresponding 1,6-imino alcohol **3i-k** in good yields. Notably, this protocol allowed the formation of **3k**, a highly functionalized structure that possess a Weinreb amide in the 1,6-inimo alcohol skeleton. Cyclobutane **3l** was also achieved, recovering 80% of the starting BCB **1l**, revealing that complex substituted cyclobutanes will be synthetizing through this method. Styrenes were successfully introduced, obtaining the desired 1,6-imino alcohols **3m-s** in excellent to good yields. *ortho*-, *meta*- or *para*-substituted styrenes afforded the corresponding

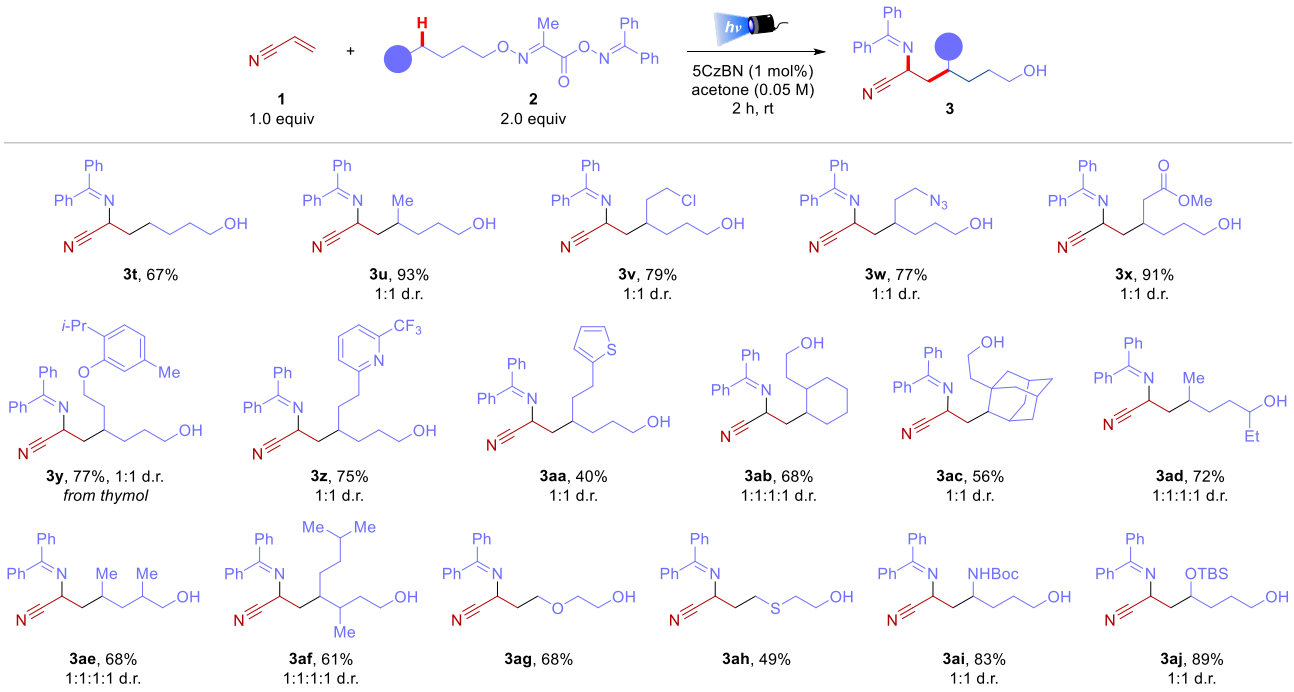
product in similar yields (**3n-p**), so the position of the substituents in the aromatic ring did not have any effect in the reactivity. Remarkably, the 1,6-imino alcohol motif was installed in various complex biomolecules and pharmaceuticals, such as *zingerone* (**3f**), *estrone* (**3g**), *flurbiprofen* (**3r**) or *gemfibrozil* (**3s**), proving that this protocol can be used for late-stage functionalization.



Scheme 1. Alkene Scope & Scaled-up. Standard conditions: **1** (0.20 mmol), **2a** (0.40 mmol), and 5CzBN (1 mol%), in dry degassed acetone (4.0 mL, 0.05 M) under blue Kessil irradiation (λ_{max} = 427 nm) for 2 hours at room temperature under inert atmosphere. [a]80% of BCB remained.

As we described in our previous work,[17] the scale-up of this transformation was performed using a homemade continuous-flow photoreactor (see Supporting Information). Thus, 1.36 mmol of **1b** was rapidly converted into the desired product **3b** in 84% isolated yield (t_R = *15 min*), similarly to batch conditions (Scheme 1).

On the other hand, different bifunctional reagents **2** were examined using acrylonitrile (**1b**) as the radical acceptor (Scheme 2). Non-functionalized alkyl alcohols were amenable to this transformation, demonstrating that not only stabilized tertiary alkyl radical precursor **2a** achieved the final 1,6-imino alcohol structures, but also non-stabilized secondary (**2c**, **2j-n**) and primary (**2b**) alkyl radical precursors afforded the desired product in good yields. Additionally, the presented methodology tolerated several functional groups, obtaining diverse 1,6-imino alcohols carrying a chlorine (**3v**) or an azide (**3w**), which can be used for further diversifications, an ester (**3x**), an ether (**3y, 3ag**) or a thioethers (**3ah**), as well as, electron-poor (**3z**) and –rich (**3aa**) heterocycles. Furthermore, *N*-Boc and silyl protected groups remained intact, and the corresponding 1,6-imino alcohols **3ai** and **3aj** were synthesized in 83 and 89% yield, respectively. However, benzylic and α-alkyne radical precursors (**2s** and **2t**) did not afforded the expected 1,6-amino alcohols, but the corresponding 1,4-amino alcohols (see supporting information).

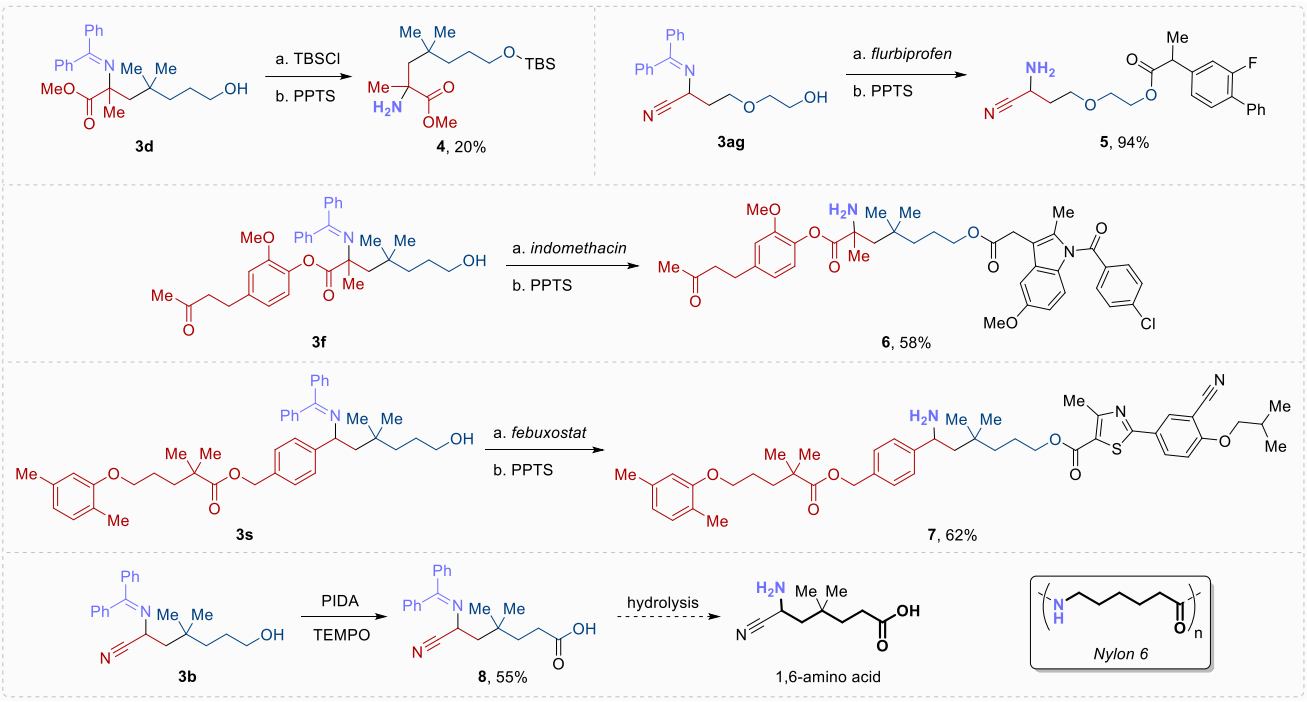


Scheme 2. Bifunctional Reagent Scope. Standard conditions: **1b** (0.20 mmol), **2** (0.40 mmol), and 5CzBN (1 mol%), in dry degassed acetone (4.0 mL, 0.05 M) under blue Kessil irradiation (λmax = 427 nm) for 2 hours at room temperature under inert atmosphere.

The utility of these 1,6-imino alcohols as important synthetic intermediate was proved with some derivatization reactions (Scheme 3). Thus, the free alcohol of **3d** was protected with *tert*-butyldimethylsilyl chloride, and the crude was directly mixed with pyridinium *para*-toluenesulfonate (PPTS) to achieve compound **4** in 20% yield in two steps. Moreover, **3f**, **3s** and **3ag** were subjected to a Steglich esterification process, and subsequent hydrolysis of the imine, to afford the *flurbiprofen* derivarite **5**, the *zingerone-indomethacin* derivative **6**, and the *gemfibrozil-feboxostat* derivative **7** in good yields. Moreover, 1,6-inimo acid **8** was obtain in 55% yield from **3b** through an oxidation step with PIDA and TEMPO. Several procedures using 6-aminohexanoic acid as linker or intermediate of more complex molecules have been reported, as well as, its use as monomer for the synthesis of Nylon 6, a versatile synthetic polymer with a wide variety of applications. Thus, this report demonstrated that it will be possible to obtain in an easy manner a library of 1,6-amino acids for its application in the synthesis of highly functionalized polymers, by the oxidation and subsequent hydrolysis of the 1,6-imino alcohols described here.

To elucidate the mechanism behind this EnT process, some mechanistic investigations were performed (see Supporting Information). The photochemical quantum yield (Φ) of this multicomponent reaction was experimentally determined using two different alkenes (**1b** and **1h**) and bifunctional reagents (**2a** and **2b**), to respectively form **3h** and **3t**. Both measurements gave a Φ value around 60, pointing a radical chain mechanism iniciated by the photocatalyst action. The presence of 4.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the standard conditions completely shut down the reaction, recovering the methyl methacrylate and the bifunctional reagent **2a** intact. Additionally, the irradiation of the mixture of **2b** and acrilonitrile in acetone with a purple Kessil lamp (λ_{max} = 390 nm), in absence of the photocatalyst, afforded the desired product **3t** in 14%. This direct excitation of the bifunctional reagent, and the TEMPO experiment, ruled out the posibility of a redox process, and proved the existance of an energy transfer event between the photocatalyst and the bifunctional reagent **2**, where the alkenes act as radical acceptors.

Figure 2 shows the proposed mechanism for the synthesis of 1,6-amino alcohols **3**, based on our previous results[17] and the experimental evidences described above. The process starts with the irradiation of 5CzBN using a blue Kessil lamp (λ_{max} = 427 nm) to generate the excited state 5CzBN* (E_T = 2.68 eV).[19] 5CzBN* interacts with the bifunctional reagent **2** to form the excited state **2*** in an energy transfer event, that induces the homolitic cleavage of the O–N bond affording the the persistent ambiphilic iminyl radical **B** and the transient alkoxy radical **A**, with extrusion of carbon dioxide and acetonitrile. Later, **A** abstracts an hydrogen from the C5 position (1,5-HAT) and generates de trasient C(sp^3)-centered radical **C**, which engages in a Giese-type addition with the alkene **1** to form the C(sp^3) radical intermediate **D**. Given the experimental quatum yield value (Φ ~ 60), the radical-radical coupling pathaway reported in several energy transfer reaction is dissmissed for this trasformation, favouring the radical-chain pathway. Thus, **D** reacts with other molecule of the bifunctional reagent **2** to achieve the desired 1,6-amino alcohol **3** and the alkoxy radical **A** with the relese of carbon dioxide and acetronitrile, regenerating the cycle.



Scheme 3. Derivatization Reactions. See the supporting information document for additional information

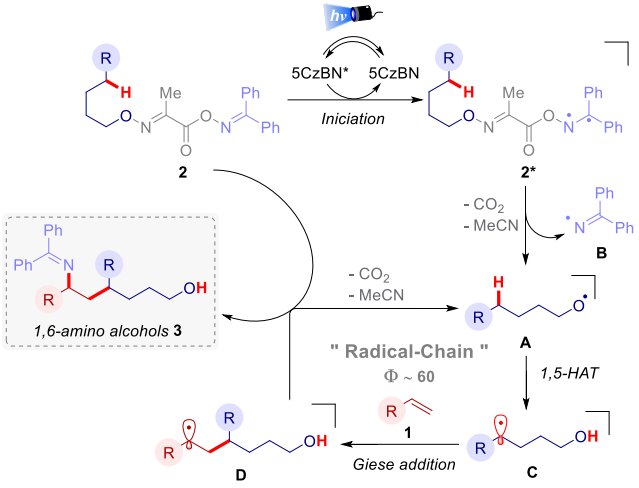


Figure 2. Proposed Mechanism.

Conclusion

In summary, an operationally simple and general 1,2-carboimination of alkenes was described to synthesize highly functionalized 1,6-amino alcohols. Not only activated alkenes with electron-withdrawing groups were amenable to this methods, but also various styrene-type alkenes, yielding excellent results. The scaled-up was efficiently achieved using a custom-built continuous-flow system, which maintained comparable reactivity to that observed in batch processing. Moreover, this multicomponent reaction proved to be highly effective for the late-stage functionalization of complex molecules, enabling the incorporation of 1,6-imino alcohol motif in various biomolecules and pharmaceuticals, including zingerone, estrone, flurbiprofen, gemfibrozil and thymol. The synthetic utility of the 1,6-imino alcohol motives was further highlighted by several derivatizations, leading to the isolation of highly functionalized molecules, such as the gemfibrozil-febuxostat compound **7**, and the synthesis of the 1,6-imino acid **8**, a potential monomer for the production of complex nylon derivatives.

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Keywords: 1,6-amino alcohols • energy transfer • 1,5-HAT • alkenes • 1,2-carboimination • late-stage functionalization

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