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Intermolecular Carboamination of Unactivated Alkenes

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Supporting Information Placeholder

ABSTRACT: Herein, we report the first example of group transfer radical addition (GTRA) of *O*-vinylhydroxylamine derivatives onto unactivated alkenes. By utilizing *O*-vinylhydroxylamine derivatives as both the *N*- and *C*-donors, this reaction enables intermolecular carboamination of unactivated alkenes in an atom economical fashion. As the process is initiated through *N*-radical addition followed by *C*-transfer, linear carboamination products are afforded. This differs from canonical radical carbofunctionalization of olefins which typically favors branched product owing to initiation by *C*-radical addition.

Over the past decades, numerous advances have been made in the realm of olefin functionalization, seminal synthetic methodologies in this area have spawned developments in the field of medicinal chemistry, polymer science, and materials science.¹ In this context, the difunctionalization of alkenes, which permits the concomitant construction of two covalent chemical bonds across the π -systems, is particularly empowering, as it allows the rapid buildup of molecular complexity from ubiquitous starting materials.² Amongst the plethora of ionic and radical methods for alkene difunctionalization, the atom transfer radical addition (ATRA) protocol pioneered by Kharasch is of particular prominence because of its compatibility with polar functionalities that are oftentimes not tolerated in transition metal catalysis.³ While the original Kharasch reaction focuses on the carbohalogenation of olefins, efforts spanning the past century have expanded the scope of similar processes, allowing incorporating of a gamut of functionalities across alkenes (Scheme 1a).⁴ Notably, the elegant contribution from the Zard group demonstrated that xanthates (dithiocarbonates) can add across alkenes in a group transfer radical addition (GTRA) using catalytic amounts of radical initiators.⁵ In general, ATRA and GTRA reactions capitalize on the homolysis of the relatively weak R'-X bond. Therefore, while GTRA-based carboamination appears as an attractive means for amine synthesis, such processes remain largely elusive owing to the inertness of C-N bonds as well as the potential deactivating effects of nucleophilic nitrogens on transition metals (Scheme 1b).

Since the seminal work of Wolfe, reports on olefin carbomaination exclusively featured intramolecular annulative reactions.⁶ The intermolecular variant of the process has only received attention from the synthetic community recently. Elegant works emanating from the groups of Rovis,⁷ Glorius,⁸ Liu⁹ and Engle¹⁰ demonstrated the tremendous potential of intermolecular olefin carboamination as a convenient gateway to access diverse arrays of nitrogen containing scaffolds. Nonetheless, these prior work generally require activated alkenes or substrates with tethered

Scheme 1. Intermolecular carboamination of unactivated alkenes



chelation groups. In addition, the ionic nature of these reactions potentially pose chemoselectivity issues when applied to densely functionalized substrates, particularly those comprising polar moieties. On the other hand, a radical-initiated alkene-carboamination method offers an attractive means to circumvent these limitations (Scheme 1c).¹¹ A few examples of such reaction manifold are known, however, the majority of reported protocols generate branched products via the *C*-radical initiation, ^{11a-c} with only sporadic examples of multicomponent reactions that favor linear structural isomers via *N*-radical initiation.^{11d-e} Additionally, known methods of radical alkene carboamination are often plagued by low atom economy and narrow scope with respect to alkenes. Functionalization of unactivated aliphatic alkenes remains virtually unexplored. Homolysis of C–N bonds followed

by the addition of the resulting radicals onto olefins appears to be the most direct means to achieve carboamination. However, the inertness of C–N $\,$

Table 1. Reaction conditions optimization^a



^{*a*}Reaction conditions: **1a-1** (0.1 mmol), **2a** (0.5 mmol), H₂O (8.5 mmol), photocatalyst (0.2 mol %) in solvent (1 ml), irradiating with 15 W blue LEDs under N₂ atmosphere at room temperature for 12 hours. NMR yields were indicated. ^{*b*}6.5 equiv of **2a** was employed. ^{*c*}**1a** was used. ^{*d*}Without H₂O or light irradiation.

bonds presents a formidable challenge (*vide supra*). In 2010, Renaud reported a solution to this long-standing problem by taking advantage of desulfonylative azide transfer manifold (Scheme 1d).¹² Renaud's inspiring study coupled with our interest on *N*-radical generation through visible-light photosensitized N–O bond cleavage¹ prompted us to investigate the use of *O*vinylhydroxylamine as a radical progenitor in GTRA reaction with alkenes. We hypothesized such a system may be advantageous for the following reasons: i) the N–O moieties have a well-documented propensity to engage in photo-mediated radical generation via either homolytic cleavage or SET/mesolysis pathway;¹⁴ ii) the enol part of this molecule could tautomerize and act as *C*-donors (*e.g.*, as radical receptors or through radical-polar crossover pathways) (Scheme 1e).

Initially, the visible-light-promoted reaction between Ovinylhydroxylamine derivative 1a-1 and ethyl vinyl ether 2a was probed (Table 1). Gratifyingly, by using $[Ir(dF(CF_3)ppy)_2(bpy)](PF_6)$ as a photocatalyst, the reaction proceeded smoothly at room temperature in aqueous MeCN under the irradiation of blue LEDs. The carboamination product 4a-1 was afforded in 62% NMR yield. Intriguingly, formation of this linear adduct indicated reaction initiation by N-radical addition. Exchanging [Ir(dF(CF₃)ppy)₂(bpy)](PF₆) for photocatalysts that are more reducing in their excited states such as fac-Ir(ppy)₃ $(E_{1/2}^{red} [Ir^{IV}/*Ir^{III}] = -1.73 \text{ V versus SCE}), \text{ eosin Y } (E_{1/2}^{red})$ $[EY^{+}/EY^{*}] = -1.11$ V versus SCE) led to diminished yields or no desired product formation. The observation appears counterintuitive at first, given the prior work on the oxidative of photocatalysts by redox-active quenching Nhydroxyphthalimide derivatives. However, it may be explained by the possible involvement of triplet energy transfer process in this reaction.¹⁵ By fine tuning the reaction stoichiometry, the NMR yield of product 4a-1 could be increased to 68%. After extensive experimentation, the 4-methylphthaloyl (abbreviate as Phth^{Me}) derivative 1a were eventually identified to be the optimal choice in terms of reaction efficiency, which afforded the desired product 4a in 71% NMR yield (see SI for details). Control experiments with respect to each reaction parameter further demonstrated the

necessity of H₂O, light irradiation as well as photocatalyst for this transformation.

With the optimized reaction conditions in hand, we proceeded to investigate the scope of this transformation. At the first, a variety of O-vinylhydroxylamine derivatives were examined with 2a as the reaction partner (Table 2). It was found that electrondeficient aromatic substrates (e.g., those with arenes substituted with halogen atoms or trifluoromethyl) delivered products efficiently (4f-4h), while those with electron-donating groups tended to afford products in moderate yields (4a-4e). In addition, fused aromatic substrate could also be used, albeit providing the desired product 4i in a lower yield. Gratifyingly, alkoxycarbonylsubstituted substrates were found to be viable substrates for this reaction, generating the α -ketone ester derivatives in good yields (4j-4l). The incorporation of versatile α -ketone moieties could potentially allow a diverse range of downstream synthetic transformations. Subsequently, the reaction generality with respect to alkene substrates was investigated. A variety of electron-rich alkenes such as vinyl ether and enamides were all found to readily engage methyl 2-((5-methyl-1,3-dioxoisoindolin-2-yl)oxy)acrylate 1i in the GTRA reaction. Capitalizing on such a process allowed the expedient construction of 5-amino-4hydroxy-2-oxopentanoate derivatives (4m-4r). Meanwhile, enamide-carboamination led to a series of diamine-derived α ketonester analogs (4s-4w). The chemoselectivity of this reaction is underscored by the tolerance of protic functionalities. It is also noteworthy that the reaction can be applied to 1,2- or 1,1disubstituted alkenyl ethers to generate respective products with contiguous stereocenters or tetra-substituted carbon centers, although the former was afforded with lower yields, presumably due to inefficient *N*-radical addition to internal alkenes (4x, 4y). Simple and unactivated aliphatic alkenes as well as those with remote functionalities were amenable to this transformation, albeit with moderate efficiency (4z-5b). This result prompted further explorations to improve the efficiency of the present system. The employment of para-trifluoromethylphenyl (abbreviate as PTP) derived O-vinylhydroxylamines 1h with 1-hexene afforded the desired y-amino ketone product 5c in 55% yield. Efforts in this direction eventually revealed a high reactivity of **1h** with regard to unactivated alkenes. Across the substrates examined, a diverse selection of polar functionalities such as halide, ketone, ester, amide, hydroxyl or even carboxyl group were left unscathed, in contrast to transition metal catalyzed processes which usually require protection of nucleophilic atoms (5d-5l). Pleasingly, boron and silvl functionalities were also well tolerated as showcased in the smooth formation of 5m and 5n. In comparison with allyltrimethylsilane, the reaction of the vinyl congener, however, resulted in much lower yield possibly because of the steric influence. In addition, vinylcyclohexane also participated in this reaction with ease and product 5p was furnished in 44% yield. Notably, internal aliphatic alkenes devoid of activation elements, which are notoriously recalcitrant to GTRA processes, took part in this reaction uneventfully. For example, the reaction of 1h and (Z)-3-hexene delivered the desired product 5q in synthetically useful yield. It is also of note that 1,1-disubstituted alkenes readily engaged in this reaction, thus offering an elegant method for the access of quarternary-carbon-containing y-amino ketone derivatives (5r-5v). Methylenecycloalkanes containing exo-alkene groups also proved to be suitable substrates as represented in the cases of 5u and 5v. Moreover, less reactive alkenyl moieties embedded in cycloalkane substrates could be smoothly functionalized, wherein the ring size of cycloalkenes had minimal impact on reaction yields (5w-5z). Although products 5z and 6a were obtained in relatively low yields because of severe steric congestion, these constitute rare examples of GTRA type functionalization of unactivated tri-substituted alkenes.

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Table 2. Substrate scope^a



^aSee the Supporting Information for reaction details. Isolated yields were provided. rr, regioisomeric ratio. dr, diastereomeric ratio.

In order to gain some mechanistic insights of the reaction, several radical clock experiments were conducted, which provided evidence for the radical nature of C-N bond forming process. Specifically, when 1,6-diene probe 7a was employed, only the radical annulation product 8a was observed instead of 1,2-difunctionalization products (Scheme 2a). When β -pinene was subjected to the standard reaction conditions with 1h, product 8b which resulted from β -fragmentation of cyclobutylmethyl radical was exclusively afforded (Scheme 2b). Furthermore, when 1h was treated with cycloocta-1,5-diene 7c, the 1,2-difunctionalization product 8d was formed in 10% yield accompanied by the generation of considerable amount of transannulation product 8c as well as hydroamination byproduct 8e (Scheme 2c). The radical nature of this reaction is also supported by the observation that the addition of TEMPO as a radical scavenger inhibited this transformation. Two essentially contrasting working modes of photocatalysis could be envisaged for the generation of Ncentered radicals: one follows triplet energy transfer from activated photocatalyst *Ir^{III} to 1, and the other takes place via photocatalyst-engaged single electron transfer (SET) manifold. The experimental results with different photocatalysts in the foregoing sections point to the likelihood of the triplet energy transfer model. Stern-Volmer fluorescence quenching experiments verified that the excited state *Ir^{III} was quenched effectively by 1h but not the alkene substrates. Of note, the application of radical initiator such as dilauroyl peroxide (DLP) in place of photosensitization is also feasible, while stoichiometric

amount of initiator was required for appreciable conversion (Scheme 2d). Furthermore, a quantum yield of 12.9 was identified between reaction 1j and 2a, which indicated the involvement of a chain process.¹⁶

Scheme 2. Control experiments



Based on the abovementioned control experiments, a proposed mechanism is put forth (Scheme 3). The reaction starts with the visible light sensitization of Ir^{III} catalyst to its excited state ^{*}Ir^{III}, which then undergoes triple energy transfer with *O*-

vinylhydroxylamine substrate 1. The ensuing homolytic cleavage of N–O bond in activated 1 give rise to *O*-radical I and *N*-radical II, respectively. Subsequently, the emerging electrophilic *N*radical selectively engages electron-rich alkene 2a to afford a secondary alkyl radical III. Consequently, this nucleophilic radical intermediate is disposed undergo further radical addition to substrate 1, which is comparatively electron-deficient. The following β -fragmentation of N–O bond in intermediate IV delivered the desired carboamination product 4 while regenerating *N*-radical II to enable a chain sustention process. Taken together, radical polar effect likely plays a central role in dictating the selectivity of the reaction.

Scheme 3. Proposed reaction mechanism



In summary, using *O*-vinylhydroxylamine derivatives as both the *N*- and *C*-donors under visible-light-sensitization, intermolecular carboamination of unactivated alkenes was successfully accomplished. The polarity effect underpins the exquisite regiochemical control of this process, affording linear products exclusively. In addition, this atom economical reaction features mild reaction conditions, broad scope, and high chemoselectivity. This reaction not only provides an alternative strategy for alkene-carboamination, but also enables the application of GTRA reactions to incorporate both carbon and nitrogen groups onto olefins, which proves to be elusive until the present report.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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(15) A DFT calculation of the triplet energy of substrate **1j** was conducted and the obtained E_T^{1j} (calc) = 60.1 Kcal/mol is within the range that should be accessed using [Ir(dF(CF₃)ppy)₂(bpy)](PF₆) as a triplet sensitizer (E_T = 60.4 Kcal/mol). See SI for details.

(16) The cross over experiment of 1a, 1h and 2a suggested the intermolecular delivery of N- and C-donors for this carboamination reaction. See SI for details.

