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Iminyl Radical-Mediated Controlled Hydroxyalkylation of Remote C(sp³)-H Bond via Tandem 1,5-HAT and Difunctionalization of Aryl Alkenes

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Abstract. A visible-light mediated γ -hydroxyalkylation of ketones *via* C(sp³)-H functionalization has been developed under redox neutral conditions. This protocol relies on the iminyl radical-triggered 1,5-HAT followed by oxyalkylation of alkenes, wherein C-C and C-O bonds were constructed in one step. This three-component reaction features mild conditions, wide substrate scope and excellent functional group tolerance, thus providing a facile and highly efficient access to complex valuable ketones.

Keywords: iminyl radical; 1,5-HAT; difunctionalization; multicomponent reactions; γ C-H functionalization.

The direct functionalization of $C(sp^3)$ -H bonds represents an elegant and promising strategy to modify the organic molecules. Due to their high bond strength and ubiquity, it is quite challenging to activate the specified C(sp³)-H bonds, especially remote and inert $C(sp^3)$ -H bonds in organic synthesis.^[1] Compared with the transition-metalcatalyzed $C(sp^3)$ -H activation, the radical-mediated functionalization of C(sp³)-H bonds via hydrogen atom transfer (HAT) process have received much attention owing to their mild reaction conditions, excellent selectivity control as well as avoiding the requirement of directing groups.^[2] Over the past few years, significant progress has been made in the C-,^[3] O-^[4] and N-centered^[5] radicals triggered selective C(sp³)-H bonds functionalization via HAT process. Among them, 1,5-HAT is commonly favorable pathway, wherein the newly formed C-centered radicals could be trapped by various reactive partners to form C-C or C-heteroatom bonds.^[3-6] For instance, Nevado et al recently demonstrated an iminyl radicalpromoted remote $C(sp^3)$ -H bond functionalization 1,5-HAT/intramolecular cyclization through а process, producing a variety of elaborated fused ketones (Scheme 1a).^[5b] Later on, Leonori et al disclosed an iminyl radical-induced direct yfluorination of ketones (Scheme 1b).^[5d] In the same vear, Studer reported an iminyl radical enabled yalkylation of ketones using Michael acceptors as alkylating reagents (Scheme 1c).^[5e] In those reactions, the reactive iminyl radicals could be easily generated from oxime derivatives by visible light-induced single electron transfer (SET).^[7] However, the selective C(sp³)-H bond abstraction and radical alkylation under mild conditions remains at an underexplored level. Furthermore, the development of elegant radical cascades for the construction of more complex molecules is still desirable and challenging. It is well known that the difunctionalization of alkenes is an extremely powerful tool for C-C and C-heteroatom bonds formation.^[7d,8] We questioned that whether the Ccentered radicals generated through 1,5-HAT process could engage in the difunctionalization of alkenes to provide diverse ketones. Herein, we present a visiblelight driven three-component γ -hydroxyalkylation of ketones through tandem iminyl radical-initiated 1,5-HAT and oxyalkylation of unactivated alkenes. In this transformation, water not only assists imine hydrolysis, but also serves as a nucleophile to participate the reaction.



Scheme 1. Photoinduced iminyl radical-triggered 1,5-HAT reactions.

Table 1. Optimization of reaction conditions.^[a]

Me Me 1a	20COC0 ₆ F ₅ Me + CH ₃ CN (2 mL), H ₂ O (100 equiv) 30 W blue LED, rt, 24 h, N ₂ 2a	HO Me Me O Me
Entry	Deviation of standard conditions	Yield[%] ^[b]
1	none	68
2	2 mol% of [Ru(bpy) ₃](PF ₆) ₂ as the photocatalyst	0
3	5 mol% of Eosin Y as the photocatalyst	0
4	DMF as the solvent	25
5	acetone as the solvent	46
6	THF as the solvent	40
7	1 equiv of HOAc was added	65
8	1 equiv of KOAc was added	43
9	w/o photocatalyst or light	0

^[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), photocatalyst (2 mol %) and water (20 mmol, 100.0 equiv) in 2.0 mL MeCN was irradiated by 30 W blue light-emitting diodes (LEDs) at 25 °C for 24 h under N_2 , ^[b] Isolated yield.

Based on our recent studies in iminyl radical chemistry,^[9] we initially examined the reactions of several oxime esters 1 and styrene 2a with water (100.0 equiv) as a nucleophile, using 2 mol % of fac- $[Ir(ppy)_3]$ as the photoredox catalyst in MeCN (0.1) M) under 30 W blue LED irradiation (Table 1). Primary investigations indicated that pentafluorobenzoyl oxime 1a was the most efficient iminyl radical precursor for this reaction and afforded the desired γ -hydroxyalkylated ketone **3a** in 68% yield. Other O-acyl oximes with leaving groups such as BzO, 4-CF₃BzO, 4-NO₂BzO, and AcO were less effective or inert for this reaction (see Table S1 in the Supporting Information). Thus, the oxime ester 1a and styrene 2a were chosen as the model substrates to survey other reaction parameters. The screening of photoredox catalysts demonstrated that except fac- $[Ir(ppy)_3]$, $[Ru(bpy)_3](PF_6)_2$ and Eosin Y didn't show any catalytic activity (entries 2 and 3). Among the solvents tested, DMF, acetone, and THF led to inferior yields (entries 4-6), while DCM and PhCF₃ were found to be ineffective solvents. Furthermore, the use of 1.0 equiv of HOAc or KOAc as additives did not improve the yield of **3a** (entries 7 and 8). Control experiments disclosed that both the photoredox catalyst and the light irradiation are crucial for the success of the reaction (entry 9).

With the optimal conditions in hand, we explored the scope of the styrenes with **1a** using water as a nucleophile. A variety of styrenes reacted efficiently with **1a** and water to give the corresponding products **3b-3j** in moderate to good yields (Table 2). The styrenes bearing electron-donating groups at the *para* position of the phenyl ring gave better yields than the

Table 2. Scope of the styrenes.^[a]



^[a] The reaction were carried out under the standard reaction conditions. ^[b] Yield on a 2 mmol scale is given in parentheses. ^[c] 4 mL MeCN was used.

substrates with electron-withdrawing groups (3b-e vs 3f-g). A wide range of functional groups, including halogens (3f, 3g, 3j), ether (3d), ester (3e) and a boronic acid pinacol ester (3h) all survived well under the present conditions. It is worth mentioning that 2-vinylnaphthalene 2k was the efficient substrate. affording the desired product **3k** in 53% yield, but 1vinylnaphthalene was inert for this transformation. Besides styrenes, 1,1-disubstituted olefins 21-2q were also efficient substrates, producing the corresponding products **31-3q** in 55-83% yields. It should be noted that the reaction could also be scaled up to 2 mmol, and the desired product **31** was obtained in 63 % yield. Notably, the reaction of 1-phenyl-1,3-butadiene with **1a** and water proceeded regioselectively to give the sole product **3r** in 45% yield, which was probably attributed to the stability of newly formed benzyl radical. When ethyl cinnamate 2s was subjected to the reaction system, the desired product 3s was isolated in 36% yield with excellent stereoselectivity. Satisfactorily, the olefinic 1,3-dicarbonyls 2t als delivered the desired product 3t, albeit in only 28% yield, wherein the intramolecular carbonyl groups were compatible.^[9e,10] Remarkably, the terminal olefins 2u and 2v derived from estrone participated this reaction well to provide the desired products 3u and 3v in 58% and 55% yield, respectively, which further demonstrated the potential applications of this protocol. Unfortunately, heteroaromatic styrenes, such as 2-vinylquinoline and pyridine were not applicable in this transformation (not shown).

Table 3. Scope of the oxime esters.



Subsequently, the generality of oxime esters 1 was evaluated using α -methylstyrene **2l** as the radical acceptor in the presence of water (Table 3). Gratifyingly, a series of oxime esters containing tertiary γ -C(sp³)-H bonds reacted smoothly with **2** and water to give the target products 4a-4g in moderate yields. The exclusive formation of 4a indicated that the iminyl radical H-abstraction of tertiary C-H bonds is more favorable than secondary and primary C-H bonds. Notably, the carbamate N-Boc in the oxime ester was compatible with the reaction conditions, whereas the N-Cbz substrate afforded the deprotected product 4f. It is noteworthy that the oxime esters having a phenyl or thiophen-2yl substituent at the α -position delivered the cycloketone 4h' or 4i' as sole product in 75% and 70% yields, respectively, which suggested that the intramolecular radical cyclization process is preferred over the intermolecular radical addition.^[5b] The oxime esters with secondary γ -C(sp³)-H bonds also gave the anticipated products (4j and 4k), but in relatively lower yields. Satisfactorily, the





^[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), *fac*-[Ir(ppy)₃] (2 mol %) and alcohols (2 mmol, 10.0 equiv) in 2.0 mL MeCN was irradiated by 30 W blue LEDs at 25 °C for 24 h under N₂, After the reaction completed, 0.5 mL water was added and the mixture was stirred at room temperature for 1 h. Isolated yield.

functionalization of benzylic $C(sp^3)$ -H bonds in oxime esters also proceeded smoothly to furnish the desired products **4l** and **4m** in 47% and 60% yields, respectively. However, oxime ester **10** having primary C-H bond did not gave the desired product.

Finally, we examined the scope of O nucleophiles in our oxyalkylation strategy (Table 4). Besides water, the common alcohols such as MeOH, EtOH, ⁱPrOH, and BnOH were also efficient nucleophiles, affording the corresponding products **5a-5b** in moderate yields. Unfortunately, the sterically hindered alcohols, amines or indoles failed to give any desired products (not shown).

To verify the probable mechanism of this reaction, radical trapping experiments were conducted carefully (eqs 1 and 2). Addition of TEMPO (1.0-equiv) to the reaction of **1a** and **2a** with water dramatically decreased the yield of **3a** and the adduct **6a** was isolated in 56% yield. These results indicated that the C-centered radical generated through 1,5-HAT should be involved in this transformation. Furthermore, the addition of BHT (1.0 equiv) also suppressed this reaction completely. On the other hand, when **1a** and (1-cyclopropylvinyl)benzene **2w** were used as the substrates, the ring expanded product **7a** was isolated in 33% yield as sole product, which provided further evidence for a radical pathway (eq 3).



Based on the above results and literatures, a possible mechanism is proposed in Scheme 2. First, the Ir^{III} is excited to Ir^{III}* upon visible-light irradiation. Subsequently, single-electron reduction of **1a** by Ir^{III}* affords the iminyl radical **I** through N-O bond cleavage and delivers the oxidized photocatalyst



Scheme 2. Proposed mechanism.

Ir^{IV}.^[11] Then, iminyl radical **I** triggers a 1.5-hydrogen atom transfer to give the C-centered radical II. The radical II attacks the C=C bond of styrene 2a regioselectively to furnish the benzyl radial III, which is oxidized by Ir^{IV} to give the carbocation intermediate IV and regenerates the photocatalyst Ir^{III}. Finally, nucleophilic attack of H₂O onto the cation **IV** followed by hydrolysis leads the to γhydroxyalkylated ketone **3a**. Finally, we also determined a quantum yield of 0.13 for the reaction. The low quantum yield and an on/off studies were consistent with the proposed absence of a chain process (For details, see the Supporting Information).^[11c]

In summary, we have developed the first visiblelight driven three-component γ -hydroxyalkylation of ketones under concise, redox neutral conditions. In this protocol, tandem iminyl radical-triggered 1,5-HAT and subsequent oxyalkylation of unactivated alkenes enabled the controlled γ -C(sp³)-H bonds functionalization of ketones. Besides water, simple alcohols were also efficient nucleophiles, leading to the corresponding γ -carboetherification of ketones in good yields. Further studies to explore new remote C(sp³)-H bond functionalization reactions by merging radical chemistry are currently underway in our laboratory.

Experimental Section

General procedure for iminyl radical-mediated controlled hydroxyalkylation of remote $C(sp^3)$ -H bond: An ovendried 10 mL reaction tube equipped with a magnetic stir bar was charged with oximes **1** (0.2 mmol, 1.0 equiv), *fac*-[Ir(ppy)₃] (0.004 mmol, 0.02 equiv), then the tube was evacuated and backfilled with nitrogen (three times). Subsequently, alkene (0.4 mmol, 2.0 equiv), 2.0 mL of MeCN and 0.36 mL of distilled water were injected into the tube by syringe under nitrogen atmosphere. The reaction mixture was stirred under the irradiation of a 30 W Blue LEDs at room temperature for 24 h. After reaction completed, the mixture was quenched with brine and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and concentrated in *vacuo*. Purification of the crude product by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1 to 2:1) to give the corresponding products **3** or **4** in yields list in Table 2 and Table 3.

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