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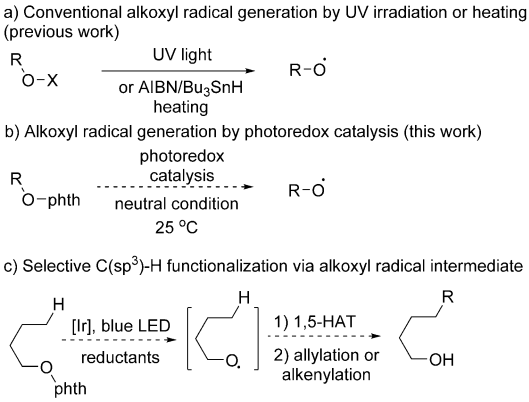
Generation of Alkoxyl Radicals by Photoredox Catalysis Enables Selective C(sp^3)–H Functionalization under Mild Reaction Conditions

*Jing Zhang, Yang Li, Fuyuan Zhang, Chenchen Hu, and Yiyun Chen**

Abstract: *Reported herein is the first visible-light-induced formation of alkoxyl radicals from N-alkoxyphthalimides, and the Hantzsch ester as the reductant is crucial for the reaction. The selective hydrogen atom abstraction by the alkoxyl radical enables C(sp^3)–H allylation and alkenylation reactions under mild reaction conditions at room temperature. Broad substrate variations, including a structurally complexed steroid, undergo the C(sp^3)–H functionalization reaction effectively with high regio- and chemoselectivity.*

The alkoxyl radical is a pivotal intermediate in chemical and biological studies, and it is not only useful for mechanistic investigations,[1] but also leads to various useful organic transformations.[2] While alkoxyl radical chemistry has been widely utilized in organic synthesis for decades, it remains a formidable challenge to generate alkoxyl radicals bearing sensitive functional groups under mild reaction conditions. Nitrites,[3] nitrates,[4] hypohalites,[5] sulphenates,[6] and *N*-alkoxylpyridine-2-thiones[7] are widely used alkoxyl radical precursors, however, they are either unstable or prepared under conditions which are incompatible with many functional groups. N-alkoxyphthalimides, in contrast, are known to be bench-stable and easily prepared from alcohols with good functional-group compatibility.[8,9] However, the conventional generation of alkoxyl radicals requires relatively harsh reaction conditions.[2,10] For example, heating conditions with azodiisobutyronitrile/tributyltin hydride is required for N-alkoxyphthalimides to generate alkoxyl radicals,[8] and compromises its synthetic scope and functional-group compatibilities (Scheme 1 a). Recently, visible-light catalysis has provided a useful new entry to the initiation of radical reactions under mild reaction conditions with good functional-group compatibility, however, alkoxyl radical generation under photoredox conditions is unknown (Scheme 1 b).[11,12]

The utilization of unactivated C(sp^3)–H bonds to engage in new C–C bond formation is desirable, but it is difficult to control the regioselectivity and chemoselectivity.[13] The alkoxyl radical easily activates C–H bonds by a selective intramolecular 1,5-hydrogen atom transfer (1,5-HAT) reaction because of the higher oxygen–hydrogen bond energy.[14] However, compared to the widely used C(sp^3)–H functionalization strategy with transition metals, an efficient intermolecular C–C bond formation after an alkoxyl radical 1,5-HAT is problematic and very difficult.[15,16] In previously reported 1,5-HAT reactions induced by alkoxyl radicals, reductive hydrogenations, oxidative cyclizations, and other carbon–heteroatom bond formations are dominant,[8,17] and the trapping of a C(sp^3) radical intermediate for efficient C–C bond coupling reaction is very limited.[16] Herein we report the first selective C(sp^3)–H allylation and alkenylation reactions enabled by an alkoxyl radical 1,5-HAT under mild photoredox conditions (Scheme 1 c).



Scheme 1. Generation of alkoxyl radicals enables selective C(sp^3)–H functionalization. AIBN = 2,2′-azobis(2-methylpropionitrile).

By using the N-alkoxyphthalimide **1** and allyl sulfone **2** as the model substrates,[18] we first tested [Ru(bpy)$_3$](PF$_6$)$_2$ ($E^0_{1/2}{}^{II/I} = -1.33$ V vs. SCE in MeCN)[19] as the photocatalyst under blue LED ($\lambda_{max} = 468 \pm 25$ nm) irradiation (Table 1). After screening various reaction conditions, including reductants and solvents (see Table S1 in the Supporting Information), we gratifyingly observed the desired C(sp^3)–H allylation adduct **3** in 75% yield by using diisopropylethylamine/Hantzsch ester as reductants in 1,4-dioxane (entry 1). We then optimized the concentration of the reaction and found that 0.1 M of **1** is optimal for the reaction (entries 2 and 3). The use of iridium-based photocatalysts, [Ir(dtbbpy)(bpy)$_2$]PF$_6$ ($E^0_{1/2}{}^{III/II} = -1.51$ V vs. SCE in MeCN)[20] and *fac*-[Ir(ppy)$_3$] ($E^0_{1/2}{}^{III/II} = -2.19$ V vs. SCE in MeCN),[21] accelerate the reaction such that the reaction is complete after 3 hours, and the use of tributylamine increases the product yield to 77% (entries 4–6). The removal of the Hantzsch ester surprisingly shuts down

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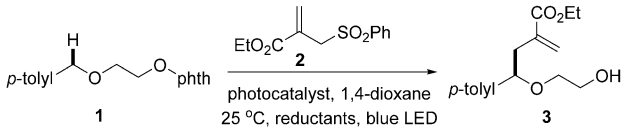
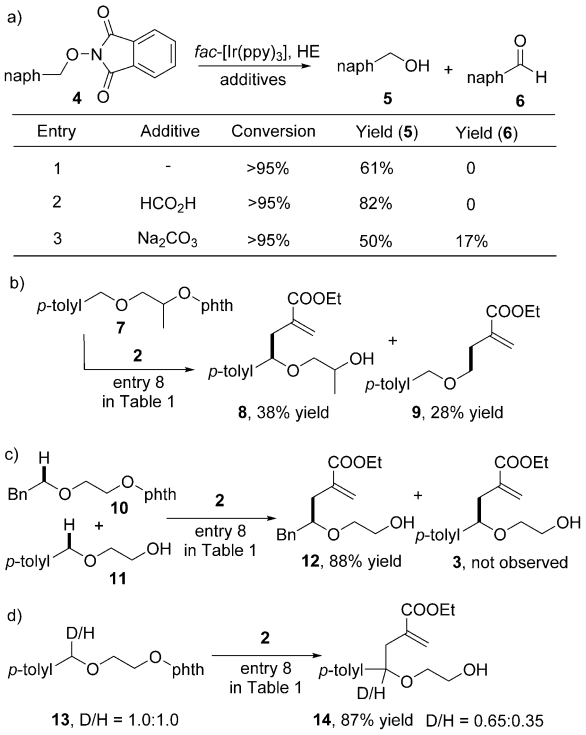
Table 1: Optimization of the alkoxyl radical enabled C(sp^3)–H functionalization.



Entry	Reaction conditions[a]	*t* [h]	Conv. [%][b]	Yield [%][b]
1	$[Ru(bpy)_3](PF_6)_2$, iPr_2NEt, HE	24	>95	75
2	entry 1, 0.05 M of **1**	24	91	71
3	entry 1, 0.2 M of **1**	24	66	56
4	$[Ir(dtbbpy)(ppy)_2]PF_6$, iPr_2NEt, HE	3	>95	65
5	*fac*-$[Ir(ppy)_3]$, iPr_2NEt, HE	3	>95	68
6	*fac*-$[Ir(ppy)_3]$, nBu_3N, HE	3	>95	77
7	*fac*-$[Ir(ppy)_3]$, nBu_3N	24	<5	0
8	*fac*-$[Ir(ppy)_3]$, HE	3	>95	94 (90)
9[c]	*fac*-$[Ir(ppy)_3]$, *N*-Me HE	3	<5	0
10[c]	*fac*-$[Ir(ppy)_3]$, BNAH	3	<5	0

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.30 mmol), photocatalyst (0.001 mmol), Hantzsch ester (HE, 0.15 mmol), and additives (0.20 mmol) in 1.0 mL 1,4-dioxane under nitrogen with 468 nm LED irradiation. [b] Conversions and yields were determined by ^1H NMR analysis. Yields of isolated products are given within parentheses. [c] *N*-Me HE (0.15 mmol), or BNAH (0.15 mmol) was used as the reductant. bpy = 2,2′-bipyridine, phth = phthalimide, ppy = phenylpyridine.



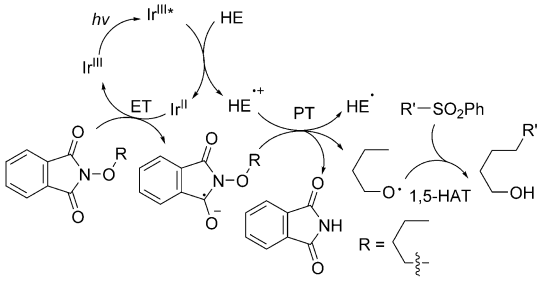
Scheme 2. Mechanistic investigations of the alkoxyl radical enabled C(sp^3)–H functionalization. HE = Hanztsch ester.

the reaction (entry 7), while the removal of the tributylamine affords an optimal 94% yield (90% yield of isolated product; entry 8). Other analogues of the Hantzsch ester, such as *N*-methyl Hantzsch ester (*N*-Me HE) or 1-benzyl-1,4-dihydronicotinamide (BNAH), are not effective (entries 9 and 10). The light irradiation and photocatalyst are both important for the reaction (see Table S1).

To gain mechanistic insights on this novel alkoxyl radical formation, we first tested the 1-naphthalene-substituted *N*-alkoxyphthalimide **4**, which does not have δ-C–H bonds. Under the optimized reaction conditions and without allyl acceptors, we observed the 1-naphthalenylmethanol **5** as the alkoxyl radical reduction adduct in 61% yield (Scheme 2a, entry 1). When formic acid is added to the reaction, **5** is obtained in an increased yield of 82% (entry 2). Interestingly, when the sodium carbonate base is added, the yield of **5** is decreased to 50%, and in addition, the 1-naphthaldehyde **6** is observed in 17% yield (entry 3). As the formation of the 1-naphthaldehyde is due to the intramolecular elimination of the N-alkoxyphthalimide radical anion,[11] these results collectively suggest that the protonation of the N-alkoxyphthalimide radical anion is important for the alkoxyl radical formation, and is similar to the coordination of the N-alkoxyphthalimide radical anion by tributyltin in the AIBN/Bu_3SnH system.[8,22]

We also carried out luminescence quenching experiments with *fac*-$[Ir(ppy)_3]$. The Hantzsch ester effectively quenches the photoexcited *fac*-$[Ir(ppy)_3]$*, and suggests that the reductive quenching is the major reaction pathway to generate the Ir^{II} intermediate.[23] When the N-alkoxyphthalimide **7** is used, we observe allylation at the δ-C(sp^3)–H position (**8**) together with the allylation adduct **9**, which is missing a two-carbon unit, by elimination of the acetaldehyde molecule, a characteristic β-fragmentation of the alkoxyl radical (Scheme 2b).[24] We also carried out crossover experiments to explore whether this C(sp^3)–H activation occurs through intramolecular or intermolecular HAT (Scheme 2c). When the N-alkoxyphthalimide **10** and the alcohol **11** are both subjected to the reaction conditions, we only obtain the allylation adduct **12** in 88% yield, and **3** is not observed. We also prepared the deuterium-substituted N-alkoxyphthalimide **13** (D/H = 1:1) and subjected it to the reaction conditions (Scheme 2d). The allylation adduct **14** is obtained with D/H = 0.65:0.35, and the different migratory aptitudes between the deuterium and hydrogen further provides evidence for the alkoxyl radical 1,5-HAT.

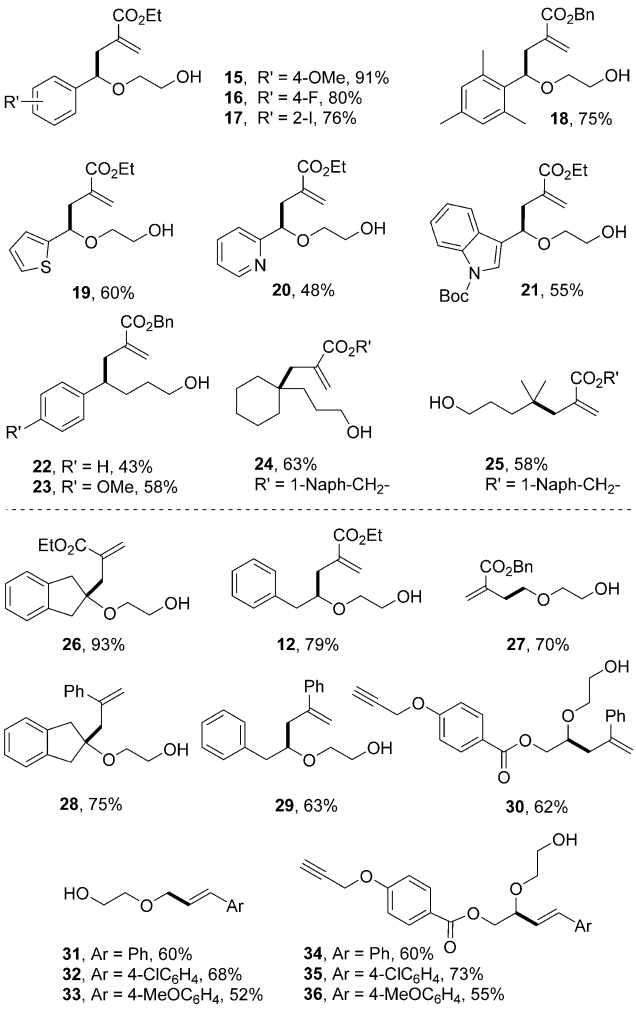
Based on mechanistic investigations above, we propose that *fac*-$[Ir(ppy)_3]$ is photoexcited to *fac*-$[Ir(ppy)_3]$* and reduced by the Hantzsch ester to Ir^{II} (Scheme 3).[25] The resulting Ir^{II} intermediate reduces the N-alkoxyphthalimide



Scheme 3. Mechanistic proposal of the alkoxyl radical enabled C(sp^3)–H functionalization.

by single-electron transfer to yield the N-alkoxyphthalimide radical anion, which is further protonated by the Hantzsch ester radical cation to facilitate the formation of the alkoxyl radical.[26] Finally, the alkoxyl radical undergoes 1,5-HAT reaction and subsequent intermolecular carbon radical trapping to yield the C–C bond-coupling adduct. In the photoredox system, the Hantzsch ester is crucial for both the electron transfer and proton transfer of the reaction, and may explain the inhibition of the reaction when it is removed.[27]

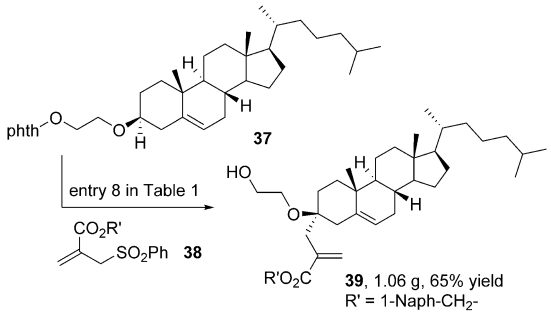
We next explored the substrate scope and found that the reaction works well for α-heteroatom-activated C–H bonds, such as with *para*-methoxy substitution, to give the allylated **15** in 91% yield (reaction conditions: entry 8 in Table 1), whereas the *para*-fluoro and *ortho*-iodo substituents gave **16** (80%) and **17** (76%), respectively (Scheme 4). Notably, this δ-C(sp^3)–H functionalization is not affected by the steric bulk on the aryl ring, that is, the 2,4,6-trimethyl-substituted arene **18** is obtained in 75% yield. We explored whether heterocycles could be tolerated under the reaction conditions, a substrate class with which many C(sp^3)–H activation methods encounter difficulties.[28] The thiophene-, pyridine-, and indole-containing heterocycles all react smoothly to give the C(sp^3)–H allylation adducts **19**–**21**, with slightly decreased reaction yields. The α-heteroatom activation is not necessary for the reaction and the benzyl C–H bonds react to give **22** and **23** in good yields.[29] The unactivated tertiary C–H bonds also react smoothly to give **24** and **25** in 63% and 58% yield, respectively,[30] as they are slightly less reactive than those with neighboring activating groups.[31]



Scheme 4. Substrate scope of the alkoxyl radical enabled C(sp^3)–H functionalization. Reaction conditions: entry 8 in Table 1. Yields are those of isolated products.

As the alkoxyl radical is known to be highly reactive, we next tested the regioselectivity of the reaction (Scheme 4): The N-alkoxyphthalimide substrates with both δ- and ε-C(sp^3)–H bonds give the δ-C(sp^3)–H activation adducts **26** and **12** exclusively, and the ε-C(sp^3)–H functionalization adducts were not observed, thus showcasing the selectivity of the reaction.[32] Methine, methylene, and methyl C–H bonds activated by an oxygen atom react well to give **26**, **12,** and **27**, respectively. The allyl acceptors can be extended to phenyl-substituted allyls and give the products **28**–**30** in 62–75% yields. This C(sp^3)–H functionalization is not only applicable to C(sp^3)–C(sp^3) bond formation, but also to C(sp^3)–C(sp^2) bond formation. With aryl vinyl sulfones as the radical acceptor,[33] the C(sp^3)–H alkenylation products are obtained smoothly and exclusively with an *E* configuration under the reaction conditions depicted in entry 8 in Table 1. The vinyl sulfones substituted with phenyl, *para*-chlorophenyl, and *para*-methoxylphenyl groups react to give the alkenes **31**–**36** smoothly, among which aryl vinyl sulfones with electron-deficient substitution give higher yields.

Given the excellent regioselectivity and chemoselectivity, we tested this C(sp^3)–H allylation on site-selective C–H functionalization of complex molecules, as it represents an attractive approach for late-stage modification of complex molecules.[34] When the N-alkoxyphthalimide-substituted steroid **37** is subjected to the reaction conditions, the allylation adduct **39** is obtained stereoselectively on gram scale in 65% yield, with complete stereoretention (Scheme 5).[35]



Scheme 5. Late-stage modification of complexed molecules.

In conclusion, we have developed the first visible-light-induced formation of alkoxyl radicals from N-alkoxyphthalimides, and the Hantzsch ester plays a crucial role in the photoredox system. Activated and unactivated C(sp^3)–H bonds react to yield selective allylation and alkenylation adducts with excellent regio- and chemoselectivity under mild reaction conditions. Additional reactivity of alkoxyl radicals and their applications in modifications of complex molecules or biomolecules are under investigation in our laboratory.

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Keywords: allylic compounds · C–H functionalization · photochemistry · alkoxyl radicals · reaction mechanisms

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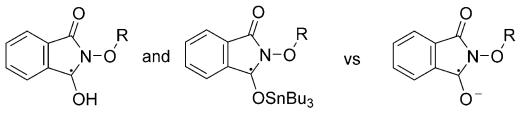

[23] In luminescence quenching experiments with *fac*-[Ir(ppy)$_3$], the K_q for the Hanztsch ester is $1.7\times10^7\,M^{-1}s^{-1}$ while for *N*-alkoxyphthalimide **1** is $1.8\times10^5\,M^{-1}s^{-1}$. When considered along with the oxidation potentials of N-alkoxyphthalimide **1** ($E^0{}_{1/2}{}^{red} = -1.35$ V vs. SCE in MeCN) and *fac*-[Ir(ppy)$_3$] ($E^0{}_{1/2}{}^{IV/III*} = -1.73$ V vs. SCE in MeCN), a minor oxidative quenching mechanism cannot be excluded (see Schemes S1–S4).

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