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Visible light-driven photocatalytic generation of sulfonamidyl radicals for alkene hydroamination of unsaturated sulfonamides

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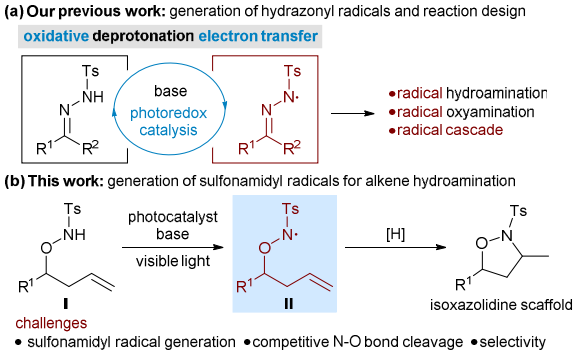
A visible light-driven photocatalytic generation of sulfonamidyl radicals and application to intramolecular alkene hydroamination has been accomplished, providing a mild and efficient approach to various functionalized isoxazolidines. The success of protocol is based on the strategy of oxidative deprotonation electron transfer by merging the base and the photocatalyst under visible light irradiation, obviating installation of photolabile handle or stoichiometric external oxidants.

Owing to the unique inherent redox properties of the excited photocatalysts, readily availability of visible light source, and simple practical implementation, synthetic photochemistry has witnessed a remarkable renaissance in the past decade.[1] Under visible light photoredox catalysis, a variety of neutral radicals and radical anions or cations could be generated in a controlled fashion under mild conditions, thus enabling various novel reaction manifolds for bond construction. In this context, the field of visible light-driven nitrogen-centred radicals (NCRs) has recently also become the subject of significant research efforts.[2] Many effective protocols have been invented for selective and controllable generation of amidyl, imidyl, iminyl, and hydrazonyl radicals from a wide variety of precursors; employing these radical species, a plethora of valuable nitrogen-containing compounds, especially nitrogen heterocycles, could be assembled by C-N bond-forming reaction, remote C-H bond activation/functionalization, and C-C single bond cleavage.[3,4] In spite of these considerable advances, research aimed at further exploration of other types of more atom-economical NCR precursors to enrich the scope is still exciting and fascinating the synthetic community.

In this regards, our group also recently developed a strategy of oxidative deprotonation electron transfer (ODET) for direct conversion of the N-H bond of β,γ-unsaturated hydrazonyl radicals by merger of suitable base and photocatalyst under visible light irradiation (Scheme 1a).[4a-e] With this activation mode, we successfully developed a range of cyclization reactions, including radical hydroamination, radical oxyamination, as well as radical cascade, providing a mild and efficient platform for dihydropyrazole and tetrahydropyridazine synthesis. The advantages of our methods lie in the readily availability of substrates, direct catalytic activation of the N-H bond, and the ease of tuning chemoselectivity by altering photocatalytic system.



Scheme 1 Visible light-driven photocatalytic generation of nitrogen-centered radicals and reaction design.

On the basis of these works, we attempt to expand our ODET activation strategy to include N-sulfonyl-O-butenyl amines of type **I** (Scheme 1b). If it works, in a similar fashion, the produced key sulfonamidyl radical **II** would cyclize onto the pendant olefin moiety to enable an intramolecular radical hydroamination reaction, when the subsequently formed carbon-centred radical intermediate traps a hydrogen atom. Notably, the achievement of this reaction would provide a complementary method for the construction of privileged isoxazolidine scaffolds that are typically synthesized by means of thermal 1,3-dipolar cycloaddition of nitrones or cyclization of unsaturated hydroxylamines.[5] It should be noted that several

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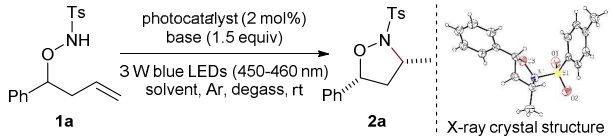
elegant works from the Chemler group demonstrated that these sulfonamides could undergo copper-catalyzed aminooxygenation and diamination at elevated temperature in the presence of stoichiometric oxidants.[6] Han et al. disclosed that TEMPO-mediated or copper-catalyzed iminoxyl radical-based radical cyclizations of unsaturated ketoximes provided a powerful alternative access to isoxazoline derivatives.[7] On the contrary, our redox neutral process avoids the need for stoichiometric external oxidants, and thus might suppress the competitive scission of N-O bond.[8]

Table 1 Condition optimization[a]

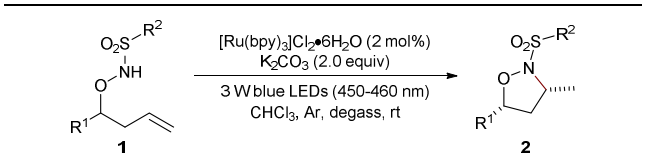


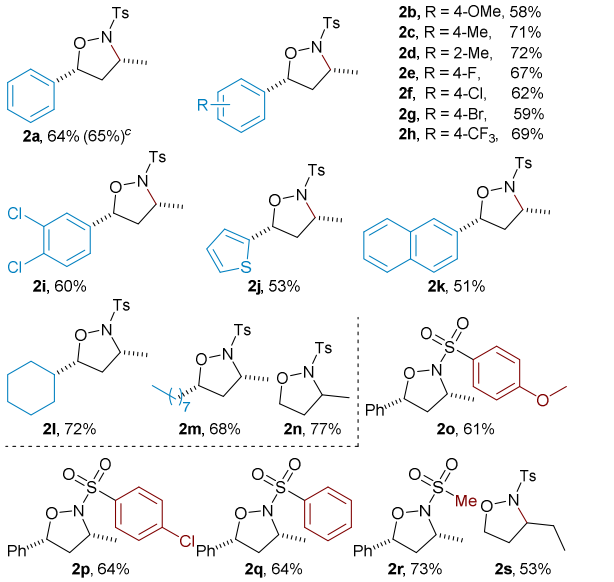
Entry	Photocatalyst	Solvent	Base	Yield[b] (%)
1	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	NaOH	32
2	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	K_2CO_3	61
3	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	^{t}BuOK	43
4	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	K_2HPO_4	53
5	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	KOH	32
6	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	Cs_2CO_3	42
7	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	DBU	38
8	Mes-AcrClO$_4$	$CHCl_3$	K_2CO_3	trace
9	*fac*-Ir(ppy)$_3$	$CHCl_3$	K_2CO_3	47
10	Ir(ppy)$_2$bpyPF$_6$	$CHCl_3$	K_2CO_3	56
11	$[Ru(phen)_3]Cl_2$	$CHCl_3$	K_2CO_3	36
12	$[Ru(bpy)_3]Cl_2•6H_2O$	CH_2Cl_2	K_2CO_3	39
13	$[Ru(bpy)_3]Cl_2•6H_2O$	MeOH	K_2CO_3	trace
14	$[Ru(bpy)_3]Cl_2•6H_2O$	H_2O	K_2CO_3	trace
15[c]	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	K_2CO_3	69(64)[d]
16[c,e]	-	$CHCl_3$	K_2CO_3	N.R.
17[f]	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	-	N.R.
18[c, g]	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	K_2CO_3	N.R.
19[h]	$[Ru(bpy)_3]Cl_2•6H_2O$	$CHCl_3$	K_2CO_3	19[d]

[a] Reaction conditions: **1a** (0.1 mmol), photocatalyst (2 mol%), and base (1.5 equiv) in 1.5 mL of solvent at rt under irradiation of 3 W blue LEDs for 24 h. [b] Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c] 2.0 equiv of K_2CO_3 was used. [d] Isolated yield. [e] Without photocatalyst. [f] Without base. [g] Without visible light irradiation. N.R. = no reaction. [h] Without degass.

Initially, we selected N-sulfonyl-O-butenyl hydroxylamine **1a** as the model substrate, and examine the feasibility of the designed reaction under our previous conditions for hydroamination of β,γ-unsaturated hydrazones.[4a] A set of representative results are summarized in Table 1.[9] To our delight, employing NaOH (1.5 equiv) as a base and $[Ru(bpy)_3]Cl_2•6H_2O$ (2 mol%) as a photocatalys in $CHCl_3$ under irradiation of 3 W blue LEDs, the desired radical hydroamination reaction did indeed work to give hydroamination product **2a** with 32% NMR yield and excellent diastereoselectivity (entry 1).[10] The 3,5-*cis* diastereoselectivity was unambiguously determined by single crystal X-ray crystallographic analysis.[11] The moderate yield was due to the formation of trace amount of ketone resulted from the N-O bond cleavage, and some other unidentified side products. Then, we proceeded to optimize conditions to improve the yield. In accordance with our previous results,[4] the base played an important role on the reaction, and K_2CO_3 proved to be the best one with **2a** being formed in 61% yield (entry 2 vs entries 3-7). With K_2CO_3 as base, we briefly examined several other commonly used photocatalysts, and $[Ru(bpy)_3]Cl_2•6H_2O$ is still superior over others (entries 8-11). A simple evaluation of some other solvents confirmed the significance of $CHCl_3$, suggesting that $CHCl_3$ might serve not only as reaction media but also as a hydrogen source (entries 12-13). Though ruthenium complex hexahydrate proved be the best catalyst, the reaction did not work at all in water as solvent (entry 14). A slight increase of yield could be obtained when 2.0 equiv of K_2CO_3 was used, giving **2a** in 64 % isolated yield (entry 15). Notably, control and comparison experiments that are performed without photocatalyst, base, light irradiation or degass did not give any desired product (entries 16-19), confirming that the observed reactivity was indeed due to the visible light-driven activation of **1a** via the ODET strategy.

Table 2 Substrate scope[a,b]





[a] Reaction conditions: **1** (0.2 mmol), $[Ru(bpy)_3]Cl_2•6H_2O$ (2 mol%), K_2CO_3 (2.0 equiv) in $CHCl_3$ (3.0 mL) at rt under irradiation of 3 W blue LEDs for 24-72 h. [b] Isolated yield. [c] Under sunlight irradiation.

With the optimal reaction conditions in hand, we proceeded to investigate the generality of this protocol by using a representative range of N-sulfonyl-O-butenyl hydroxylamines. As highlighted in Table 2, the catalytic system demonstrated widespread substrate scope and high functional group tolerance with respect to the aromatic moiety. In addition to **1a**, the reaction of substrates **1b-1d** with an electron-donating group (e.g., Me, OMe) at the *para*- or *ortho*-position of the phenyl ring reacted well to give the desired product **2b-2d** with 58-72% yields. Moreover, a set of substrates **1e-**

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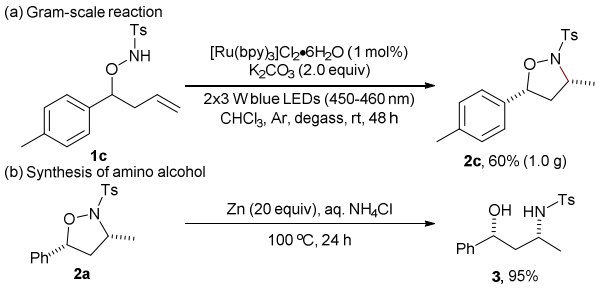
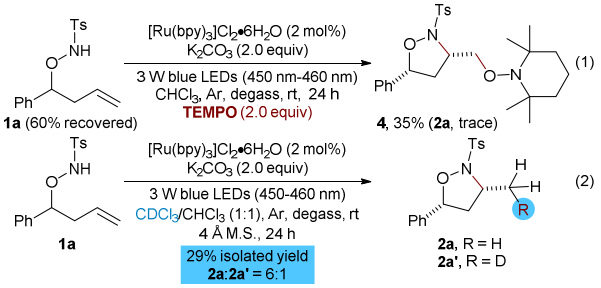
1g with halogen atoms such as F, Cl, and Br, as well as **1h** with a trifluoromethyl group at the *para*-position of the aromatic ring all underwent the desired radical hydroamination reaction smoothly to afford the corresponding products **2e-2h** in good yields (59-69%). The substitution pattern of the phenyl ring has no influence on the reaction either; multisubstituted substrate **1i** was well tolerated with isoxazolidine **2i** being isolated in 60% yield. The reaction of 2-thienyl- and 2-naphthyl-substituted hydroxylamines **1j** and **1k** also worked well to produce **2j** and **2k** in 53% and 51% yields, respectively. As demonstrated in the synthesis of isoxazolidines **2l-2n**, a series of hydroxylamines **1l-1m** bearing cyclic or linear aliphatic moiety, or even simple substrate **1n** proved to be suitable for the reaction, leading to good yields. Notably, structural variation of the sulfone moiety has no obvious effect on the reaction either. For instance, the reaction of substrates **1o** and **1p** with an electron-donating (e.g., OMe) group or electron-withdrawing (e.g., Cl) group on the aromatic ring proceeded nicely, affording **2o** and **2p** in 64% yield. Changing the tosyl (Ts) group to a methanesulfonyl (Ms) group also gave rise to the expected product **2r** in 73% yield. Note that efficient synthesis of **2a** could also be achieved under less than 6 h of total sunlight exposure.[9] The reaction of substrate **1s** also worked well to give **2s** in 53% yield. Remarkably, all of the 3,5-disubstituted isoxazolidine products were obtained as a single diastereomer, and assigned to be 3,5-*cis* based on NMR analysis and in analogy with **2a**. As a limitation of our system, substrate with longer chain did not react under the standard conditions. Attempts to remove the Ts group of **2a** met failure at the current stage.[9]

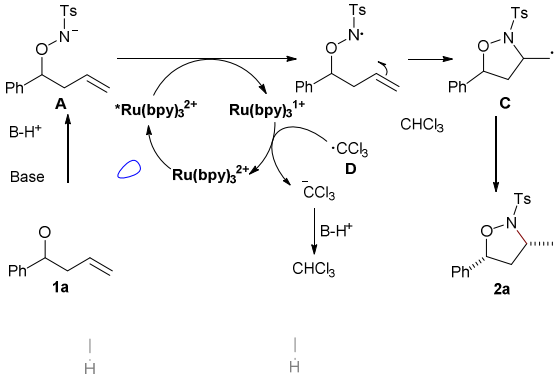


Scheme 2 Synthetic application.

To further illustrate the synthetic utility of the present reaction, a gram-scale reaction of hydroxylamine **1c** was also performed in the presence of 1 mol% of catalyst loading, and the reaction also proceeded well to give the product **2c** in 60% yield (Scheme 2a). As demonstrated in the case of **2a**, the N-O bond of isoxazolidines can be easily reductively cleaved by Zn in a solution of NH_4Cl to give valuable building block 1,3-amino alcohol **3** in excellent yield (Scheme 2b).



To assist the understanding of the mechanism, we first performed the model reaction of **1a** in the presence of stoichiometric radical scavenger TEMPO under the standard conditions (eqn (1)). It was found that a 35% yield of TEMPO-adduct **4** was isolated, though the substrate **1a** was recovered in 60% and no desired product **2a** was detected. This observation suggested the involvement of carbon-centred radical intermediate, which should be formed upon the radical addition of nitrogen-centred radical to the alkene moiety.[4] Interestingly, when using a 1/1 mixture of $CDCl_3/CHCl_3$ as the solvent, the reaction of **1a** gave rise to a mixture of **2a** and **2a'** in 29% yield with 6:1 ratio (eqn (2)). This finding indicates that the reaction media served as hydrogen source, and the hydrogen atom transfer process should be the rate limiting step (Scheme 3). Moreover, a series of fluorescence quenching experiments with **1a** with or without K_2CO_3 were also performed; once again, it was revealed that only upon addition of base can substrate **1a** significantly quench the excited photocatalyst (see the ESI†).[9]



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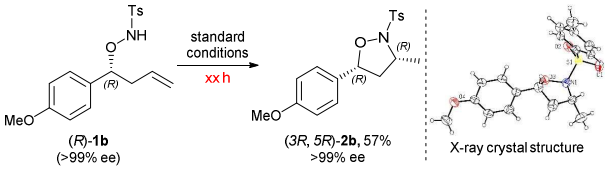
radical alkene hydroamination of unsaturated sulfonamides, we subjected the enantiopure (*R*)-**1b** to the standard conditions (Scheme 4). The expected reaction proceeded smoothly to give product **2b** as a single diastereomer in 57% yield with >99% ee. The absolute configuration of **2b** was unambiguously determined to be (*3R*, *5R*) by X-ray crystallography,[11] indicating that the labile benzylic stereocenter was not affected.



(*R*)-**1b** (>99% ee)

(*3R*, *5R*)-**2b**, 57% >99% ee

Scheme 4 Enantioselective version of visible light-driven photocatalytic alkene hydroamination.

In summary, we have described a visible light-driven photocatalytic generation of sulfonamidyl radicals for the first time. These radical species enable development of an intramolecular radical alkene hydroamination reaction, providing a mild and efficient approach to various valuable functionalized isoxazolidines. Further application of the current protocol to activation of other N-H bonds into NCRs is currently underway.

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